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EXPLOITATION AND CLINICAL TRIALS IN DEVELOPING COUNTRIES

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Abstract:

This thesis discusses comprehensively the issue of exploitation from a normative perspective specifically relating to clinical trials within developing countries using a normative definition. Exploitation is defined from an unfairness perspective as the unfair use of an individual (group of individual) by another. In order to ease the flow of the arguments within this thesis, unfairness will be assessed from two different perspectives: a procedural perspective and an outcome perspective. The procedural perspective discusses whether the procedures followed when obtaining informed consent from the potential participants fulfilled the requirements of informed consent or failed to do so. Though the use of this approach it is concluded that informed consent is not a necessary condition for the avoidance of exploitation. Similarly, it is concluded that even if morally transformative, valid consent is given by potential participants, exploitation may still be lurking in the shadows of the interaction between the trial participants and the researchers/sponsors. The outcome perspective of unfairness focuses on the effect of the interaction on the parties involved within it and whether they benefit from their interaction with each other, are not affected by it, or are actually harmed as a result of the interaction. As an extension of this argument, the thesis will also consider the post-trial perspective of the interaction. The thesis concludes that post-trial access (reasonable availability) has a very narrow view of benefit and does not ensure that there is a fair share of the benefits between the parties involved. Instead of this narrow approach, a wider, post-trial benefit approach is adopted in order to prevent

exploitation. Further discussion within the thesis will include, the requirements of an ethical review, the makeup of the review boards, and priority decision making in keeping with the current research ethics discussion in the literature.

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Chapter One: Introduction:

The performance of clinical trials necessitates the recruitment of human subjects into trials as trial participants. The necessity to involve human subjects in research has been well established a while ago. Without the involvement of human participant in clinical trials, the results obtained from research on animals or in laboratories cannot blindly be applied to human beings. Therefore new therapies have to pass through many phases before being approved for use by humans. This is done in order for the safety and efficacy of the tested agent to be proven. Usually large numbers of trial participants are recruited into phase III trials or clinical trials. These procedures have been mainly maintained in industrialized countries where regulations and rules have been put in place to monitor research involving humans with the aim of protecting participants from the risk of exploitation and the exposure to unnecessary harm from scientifically invalid or unethical research.

One of the major problems facing researchers within industrialized countries regarding the recruitment of trial participants is the increasing difficulty in recruiting the required number of participants. This is due to several reasons. The large number of clinical trials being carried out in developed countries, means that many people residing in these locations are approached either directly by their health care providers or through advertisements to take part in a given trial. Secondly, clinical trials require the recruitment of larger numbers of participants. These two points make it harder for the sponsor to recruit the required number of participants within the required time frame therefore delaying the initiation and ending of the trial. Thirdly, the population in industrialized countries usually consumes several kinds of

pharmaceutical agents on a daily basis. This means that there is a greater the chance of an interaction between the tested agent and the other agents being used by the trial participants. Fourthly, because of the tight regulations established within developed countries, the use of placebo in clinical trials is not permitted if another effective modality of treatment for the same illness already exists. Fifthly, because of the many regulations within developed countries, there are delays in the initiation of trials. Finally, the cost of these clinical trials is becoming very expensive in industrialized countries.

In an attempt to solve these problems, trial sponsors have turned to the recruitment of trial participants from developing countries. This increased attention of sponsors to developing countries is evident from the increase in the number of trials carried out in developing countries. For example GlaxoSmithKline increased the number of trials outside the US and Western Europe by 21% in 2007. Similarly, Wyeth pharmaceuticals increased its trials outside the US by 20% in 2006 (Petryna, 2009). This can also be seen through the increased use of trial participants from developing countries. According to recent industry statistics, Central-Eastern-Europe has the highest volume of patients enrolled per investigative site (6.27), followed by the Asian-Pacific region (5.78), South-Central America (4.56), and Western Europe (3.08) (Petryna, 2009: 13).

The term "developing countries" is generally used to indicate that the concerned countries have not attained a level of development considered acceptable by western countries. Hence the term is rejected by some countries as it indicates that they need to reach a level of development acceptable to the more developed countries. For the purposes of this thesis, the term "developing countries" will be used to reflect the level of basic needs, including

health care services, provided to the populations within these countries. This level is most commonly related to the country's income. There are low income developing countries struggling to provide the very basic services to its population including many basic human needs such as clean water supplies and health care services. Then there are middle income developing countries which may have basic health care services but may have difficulties with other services such as clean water supplies or sanitation. Finally there are high income developing countries with very advanced health care services but who still struggle with the issue of fair distribution and ease of access to these services. For the purposes of this thesis, the term "developing countries" will be used to cover all the different categories mentioned earlier since some of the issues which will be presented later may be replicated in different settings such as informed consent and post-trial benefits. This means that the issues regarding the possibility of exploitation of these populations within a research context exists within all these settings.

The shift in trial sponsors' interests in the performance of clinical trials within developing countries brought certain concerns to the surface especially the issue of exploitation of trial participants recruited from developing countries by sponsors from more developed countries. These concerns focus mainly on alleged accusations that the industrialized country sponsors have shifted their attention to developing countries for reasons that relate to their own benefit. Aiding factors to this shift include lack of regulations concerning the performance of clinical trials within these countries, the in-availability of treatments for many illnesses devastating these regions, the labelling of developing countries population as "virgin populations" because they do not consume any or very little pharmaceutical agents,

and the high prevalence of certain illnesses which enables the sponsors in recruiting large numbers of participants into the trials within shorter periods of time compared to industrialized countries. The main reason why this shift in trial location became a focus of discussions is the labelling of developing countries populations as being vulnerable. Many of the developing countries are still stricken with poverty and have poor health care services. There is a desperate need to improve the health care settings within those countries to try and alleviate some of suffering. The life expectancy in developing countries is shorter than that in industrialized countries by a third (Halstead, 1987). Three million lives are lost each year because of the poor health care systems as well as other factors including poverty, poor health care systems, lack of access to clean safe water, and poor sanitation. (World Bank, 2001). Almost fourteen million people die every year in developing countries from infectious diseases. The sad fact is that these deaths could be prevented if people had access to basic, affordable medications (Watkins, 2001). However, accusation of exploitation based on the vulnerability of these populations, lack of regulations within developing countries, and the shift in location of clinical trials ignores other issues which may be used to defend this shift. The prevalence of some illnesses within developing countries and the lack of treatments for these illnesses mean that clinical trials have to be performed within these settings. Hence vulnerable populations have to be recruited into these trials. Furthermore, in some cases despite the existence of treatments within other countries, these interventions cannot be blindly made available to the populations within developing countries because of many factors. From a financial perspective, the governments of some developing countries are incapable of purchasing these interventions because of their high cost. Hence shorter, more

affordable interventions need to be made available to these populations which may justify the performance of trials within these settings. On the other hand, results of trials performed within industrialized countries cannot automatically be implemented within developing countries due to malnutrition for example which may render the application of the same dosage of these interventions within developing country populations ineffective or highly toxic. In addition, the lack of regulations regarding clinical trials within developing countries has not been instated by the sponsors of the trials, nor is the high prevalence of illnesses and lack of treatment options under the control of the sponsors. Furthermore, despite all the disadvantages that surround developing countries populations, their recruitment into trials does not necessarily mean that they are being harmed, are exploited, or that they will not benefit from being recruited into the trial.

The accusation that the shift of clinical trials to developing countries is exploitative has to do more with what these trials actually focus on. Most of the trials carried out in developing countries and sponsored by industrialized countries do not address the health care needs of the developing countries or their populations. For example, about 50% of the global health research and development carried out in 1992 was undertaken by the private industry, however, less than 5% of that was spent on diseases specific to less developed countries (WHO, 1999). Also in the period extending from 1975 until 1997; of the 1233 drugs licensed worldwide, only four were developed by commercial pharmaceutical firms specifically for tropical diseases of humans (Pecoul, 1999). This means despite the fact that 90% of the global burden of illnesses exists in developing countries, only 10% of the billions spent annually on health research worldwide focuses its attention on what makes up 90% of

disease burden faced in developing countries. This is also known as the 10/90 gap (Global Forum for Health Research, 2000).

In order for us to prove that exploitation actually takes place we need to be clear about the definition of exploitation. In fact many definitions of exploitation exist (Arneson 2001). Some definitions imply a net gain by the exploiter as a necessary requirement for exploitation. This idea is emphasized in Wertheimer's quote of Tormey:

"Exploitation necessarily involves benefits or gains of some kind to someone....Exploitation resembles a zero-sum game, viz. what the exploiter gains, the exploitee loses, or minimally, for the exploiter to gain, the exploitee must lose." (Wertheimer, 1996: 10)

However, the simple gain or benefit of the exploiter does not imply that the interaction is exploitative. Indeed the effect on the other party involved in the interaction, namely the trial participants or their communities, needs to be considered as well. This is reflected in some other definitions of exploitation which relate specifically to the Kantian approach which views exploitation as the instrumental use of individuals as a means to an ends rather than as an ends in themselves. In order for us to say that exploitation occurs within interactions between the researchers/sponsors and the trial participants, we need to prove that the researchers/sponsors used the trial participants instrumentally as a means to an ends exclusively. This concept is also false as will be proven through later discussions.

According to some other definitions relating to the effect of the interaction on the trial participants, the exploited person must endure harm in order for exploitation to be said to exist within the interaction:

"Persons are exploited if (1) others secure a benefit by (2) using them as a tool or resource so as (3) to cause them serious harm." (Munzer, 1990: 171)

However, harm is not a factor that determines the existence of exploitation within an interaction. This point will be further discussed in chapter three. Still other definitions of exploitation depend on the presence of a coercive relationship:

"Exploitation forms part of an exchange of goods and services when (1) the goods and services exchanged are quite obviously not of equivalent value, and (2) one party to the exchange uses a substantial degree of coercion." (Moore, 1973: 53)

Although the presence of coercion within an interaction leads us to be suspicious about an interaction, coercion is not one of the conditions of exploitation and does not lead us to the automatically label an interaction as being exploitative.

This thesis is written from a philosophical bioethical perspective to focus on the issue of exploitation specifically relating to clinical trials within developing countries. Although the issue of exploitation has been discussed extensively in the literature, this thesis will use a normative definition of exploitation and will define exploitation from an unfairness perspective. A comprehensive analysis of the topics relevant to exploitation and the ethics of

clinical trials in developing countries will be presented. The normative definition of exploitation which will be applied within the thesis defines exploitation as the unfair use of one individual (or group of individuals) by another. This approach will be used for several reasons. To begin with, there are no hard set rules when it comes to research ethics. There are no absolute standards which allow the performance of a given trial within one country or certain part of the world and prevent it in another. Hence decisions regarding the permissibility of any given trial within developing countries (or any other country for that matter) depend on moral judgements. These judgements vary between different people and different cultures because they are based on moral judgements which assess whether a certain interaction is fair or unfair. The judgement of whether a given trials is permissible within a certain culture or region is made by a group of people charged with the responsibility of reviewing trial proposals and serving as review board members. The decisions made by these members should focus on the fairness of the interaction between both the potential trial participants and their communities on the one hand and the researchers/sponsors on the other. If exploitation is defined as “unfair use”, it follows then that the assessment of whether an interaction is exploitative or not can be answered by assessing whether an interaction if fair or unfair. Secondly, there are social influences or forces that encourage or discourage the tolerance of a given act. Thirdly, there are differences between the beliefs and cultural norms between the sponsors of the trials (from industrialised countries) and the recruited populations (from developing countries). Furthermore, exploitation does not necessarily mean the infliction of harm on the exploited person, nor does it mean the instrumental use of the exploited. Also the benefit to the so

called “exploiter”, more specifically the researcher/sponsor within this setting, does not necessarily mean that the relationship between the two parties is necessarily exploitative.

In order to justify the choice of the normative approach, clarifications need to be made regarding how unfairness is defined. To reach that goal, and simplify the flow of the arguments within this thesis, unfairness will be assessed from two different perspectives: a procedural perspective and an outcome perspective (Wertheimer, 2010). The procedural perspective, however, will be presented in a novel method. This term will not focus on the procedures followed for the approval of trial proposals as the title may imply. Instead it will be used to assess whether the procedures followed when obtaining informed consent from the potential participants fulfilled the requirements of informed consent or failed to do so. This approach is used to show that the concept of informed consent as being a necessary condition for the avoidance of exploitation is not true. Similarly, it is intended to show that a defective informed consent does not lead to the conclusion that the interaction is exploitative. The objective is to show that even if morally transformative, valid consent is given by potential participants, exploitation may still be lurking in the shadows of the interaction between the trial participants and the researchers/sponsors.

The second perspective of unfairness focuses on the outcome of the interaction and whether the parties involved benefit from their interaction with each other, are not affected by it, or are actually harmed as a result of the interaction. Hence exploitation will also be discussed from a post-trial perspective and whether the provision of post-trial treatment or any other form of benefit could be provided to the participants of the trial or their communities in

order to prevent exploitation and ensure outcome fairness. These two kinds of unfairness will be discussed separately in different chapters.

Arguments in this thesis will put forward new positions regarding the ethical requirements of benefits sharing and post-trial access linking them to exploitation. Further discussion within the thesis will include, the requirements of an ethical review, the makeup of the review boards, and priority decision making in keeping with the current research ethics discussion in the literature.

Hence the thesis will be made up of a total of six chapters including the current one. Chapter two will begin by giving a definition of exploitation and will focus on exploitation from a procedural perspective. The chapter will discuss the doctrine of informed consent and its requirements. However a broader concept of the term will be used with a focus on the validity of the consent, the factors that may influence it and how it can be improved. Furthermore the chapter will look into the issue of who should provide the informed consent: the trial participants themselves or the community leader. This issue arises particularly within developing countries given the circumstances that exist within these countries where the community is seen as a whole and the value of the individual consent does not receive the same level of importance as that seen within industrialised countries. Also the different types of documentation or proof of agreement of the potential participants that may be acceptable in developing countries will be presented. The chapter aims to argue that the limited approach to the requirements of informed consent leaves out the essence of the whole process. By focusing on how much information we should disclose to the potential participants and how we should document the consent of the participants, instead of

focusing on the method of communicating with potential participants and accepting new ways of documenting their agreement to be enrolled into a trial, we have turned the whole process into a legal one instead of the purpose it was originally created for i.e. it being a moral and ethical requirement. The chapter will conclude that in order for procedural fairness to be ensured, communication between the researchers and the potential participants need to be improved and the level of understanding of the potential participants needs to be assessed. In addition respect needs to be paid to community consent which in some societies replaces individual consent, however enough resilience needs to be applied to ensure that individuals who want to opt out of the trial are not forced into participation through the community consent. The chapter will also conclude that even when informed consent is given by the potential participants, the interaction may still be labelled as exploitative.

Chapter three will discuss outcome unfairness. Discussions will revolve around the different possible outcomes of the interaction between the potential participants and the researchers/sponsors and how each links back to exploitation. In order to assess the outcome of this interaction we need to consider all possible outcomes of the interaction and assess them against each other. However even after we do that we are still left with the question of who is the best equipped or trained to assess the acceptability of these different outcomes. I intend to show through the arguments presented within this chapter that the decision regarding the acceptability of the risks and benefits of any given trial should be done by the potential participants or at least by local review boards.

Chapter four will examine benefits that could be anticipated from the trial. This will be done from two broad perspectives: post-trial access and post-trial benefit. From a post-trial access perspective, discussions will consider the questions of who should have access to the proven intervention after the trial has ended, if any, based on the duties owed by the researchers/sponsors to the trial participants. If the provision of the proven intervention is seen as an action owed by the researchers/sponsors to their trial participants then we will have to address the issues of how long these interventions should be supplied for and to which population specifically. We will also need to address whether other groups within the community should be granted access to those proven interventions. It is intended to show in this chapter that the post-trial access approach views benefit from a very narrow perspective and may not even be practical. Hence a better approach is to adopt the post-trial benefit approach and include other forms of benefit which may not be directed to the potential participants only but may extend to include their communities.

Chapter five will focus on the role of research ethics committees in the prevention of exploitation. These review boards are known by different names. Some of these names include: institutional review boards (IRB), independent ethics committee (IEC), ethics review committees (ERC), or research ethics committees (REC). For the purposes of this thesis the term research ethics committees (REC) will be used when referring to the research ethics review boards. The role of RECs in the prevention of participant exploitation will also be discussed. The focus will be on whether the makeup of these committees aids them in performing this task or not. In addition, the issue which is frequently brought about regarding the discrepancies between the decisions of different RECs, the factors that lead to

these differences, and how they could be prevented will be discussed. It is intended to argue that these differences in decisions between different RECs should not be seen as a wrong outcome. The reasons behind these discrepancies may be the input of cultural and local beliefs rather than the process of assessment itself.

Chapter six will provide an overall summary of all the arguments presented within the preceding chapters.

Generally the thesis aims to show through argumentation that exploitation of trial participants within developing countries does not exist due to the health care settings within these countries or due to the risk of harm they may be exposed to during the trial, but rather due to the lack of social value to the communities involved. My vision is that the scope of post-trial benefit should be widened to include reductions in the 10/90 gap. By focusing our attention at improving the health care services within the hosting country and gearing our trials towards agents with potential for curing diseases burdening these countries, we can help developing countries more effectively.

Many different references will be used throughout the thesis. The selection of the references will be based on their historical importance within research ethics, their impact on the advancements of research ethics, as well as the widespread recognition.

Chapter Two: Exploitation & Procedural Unfairness

Introduction:

The most common accusation made against trials sponsored from developed countries being carried out in developing countries is that they exploit the trial participants. The most general meaning of the word “exploitation” is the use of something or someone (usually referred to as the exploited), for the advantage of another, (usually referred to as the exploiter), in an unfair way. In a clinical trial the potential exploiters may include the sponsors of the trial, the researchers, the researchers’ teams, the institution where the trial will be carried out as well as the potential beneficiaries in developed countries. On the other hand, participants of that specific trial or their entire community account for the potential person or people being exploited.

People tend to use the term exploitation rather loosely to mean different things. It can mean using someone or something for a specific purpose. For example, we can say that “the researcher exploits his intelligence while preparing for his clinical trial”. This statements does not impose any moral judgement about the character of the researcher or his actions. The action of using ones intelligence does not imply immoral behaviours because although it is driven by the benefit to the user, it does not in fact involve the use of another person but rather involves the use of a specific inanimate object or character. The researcher uses part of his own abilities in order to gain benefit. This notion is what Wertheimer defined as a

morally neutral sense of exploitation (Resnik, 2003: 235). On the other hand, the non-morally neutral sense of exploitation refers to taking unfair advantage of someone i.e. a person. Within the non-morally neutral sense of exploitation, the exploiter uses the other for the sake of self-benefit. But the mere action of use once again does not mean that exploitation exists within the interaction even if it was with the intent of gaining benefit through the interaction. There has to be another element in combination with the use of another that makes us define the use itself as being exploitative. This missing element is the “unfairness” of that use. This is the kind of exploitation that we will be concerned with here. Hence the definition of exploitation which will be used throughout this thesis will be: “A exploits B by taking unfair advantage of B”.

The normative approach to exploitation specifies two necessary conditions for an interaction to be defined as exploitative. The first condition is that the exploited person must have an element of desperation or the exploited person must be in a state where no options are available other than the exploitative interaction. Furthermore, the gain obtained by the exploiter must be morally problematic and motivated by taking opportunity of the unfair circumstances that the exploited person exists within.

This chapter will focus on the issue of procedural unfairness. Traditionally the term “procedural fairness” refers to the procedures followed by RECs during the ethical appraisal of trial proposals, and the fairness and reliability of these procedures (Wertherimer, 2010). However, the term “procedural” in this chapter will be considered from a fresh perspective. The term will be used to consider whether the procedures and processes involved in obtaining informed consent fulfil the fairness criteria. The focus of the arguments will be to

disprove the argument that defective consent is a necessary condition for unfairness and hence exploitation. Hence the chapter will focus on three perspectives relating to informed consent and procedural unfairness. The first perspective is that defective consent is not a necessary condition for exploitation. Along the same line of thought, it is emphasised that informed consent of individual potential participants does not mean that the interaction between the two can be classified as being fair and non-exploitative. Obtaining informed consent from potential participants is a requirement which needs to be fulfilled due to the ethical appraisal of trial proposals through the traditional meaning of assurance of procedural fairness. Through this process however, attention is focused on the type and kind of information that needs to be conveyed to the potential participants in order to ensure that no individual is recruited into a trial without their agreement. The second perspective of the chapter will be the essential adaptation of a shift of the researchers' emphasis on the importance of communication with the potential trial participants instead of how much and what information needs to be disclosed to the potential participants. The third perspective of the chapter will be the importance of community consent. The chapter will present an argument that within certain societies, community consent could be taken to replace individual consent if the concept of individual consent does not exist within the community or is rejected by it. This should be done to ensure respect for the different cultural and societal diversities. However, certain individuals within that community may have different perspectives about their own consent. They may either want to be excluded from the trial despite of community consent or may request to be enrolled regardless of the community's refusal to give consent. With these existing possibilities, the researchers should

accommodate for such situations. At the same time, enough attention should be paid to settings where oppressive regimes may prevent individuals within these societies from voicing their reluctance to participation in any given trial especially if the fear of social retribution exists. Hence while it is not always necessary to obtain individual consent, researchers/sponsors must respect competent refusals and ensure that the individuals have the opportunity to refuse.

In order to understand this definition of exploitation and explain why the interaction between potential participants from developing countries and the researchers/sponsors may be labelled as being unfair we need to be very clear about what “unfairness” precisely means.

Unfairness:

We mentioned earlier that the general definition of non-morally neutral exploitation is the unfair use of one person by another in order for the earlier party to gain benefit. If exploitation is linked to taking unfair advantage of another person, we need to be clear about the meaning of the word “unfair”. Hawkins and Emanuel present two basic formations that make interactions exploitative (Hawkins & Emanuel, 2008). The first one they mention refers to situations where the terms of the interactions are themselves wrongful because they are degrading and unfair. The second type of exploitative interactions focuses on the kind of vulnerabilities that surround the exploited person and which the exploiter wants to benefit from. However, both these types revolve around the same issues i.e. informed consent and how it may be affected by external factors which may place the potential

participant at a vulnerable situation and lead the researchers/sponsors to take advantage of these circumstances for their own benefit. Hence for the purposes of the discussions within this chapter another classification of unfairness will be used, one which provides an easier and broader method for assessment of “unfairness”. This method considers two different perspectives of unfairness: a procedural perspective and an outcome perspective (Wertheimer, 2010).

However, in order to ease the flow of the arguments, only one type of unfairness will be discussed in this chapter, namely procedural unfairness. Outcome unfairness will be discussed separately in the next chapter.

Procedural unfairness:

My account of procedural unfairness, as stated earlier, will focus on the procedural aspect in the process of informed consent within the interaction between the potential participants and the researchers/sponsors. Through this process, the focus becomes whether the potential participants are given enough information and time to consider the acceptability of their involvement within the interaction. To ensure procedural fairness we need to consider the agreement between the parties involved in the interaction. In clinical trials, the researchers consent to partake in their relationship with the potential participants since they are the ones initiating the interaction and trying to recruit participants. On the other hand, the participants can either agree to participate, refuse to join the trial, or be recruited without their knowledge. Therefore some interactions may be consensual meaning that the potential participants agree to interact with the researcher/sponsor. Alternatively, the

interaction may be non-consensual where potential participants are entered into the interactions without their consent or without their consent being morally transformative. Hence the arguments which follow in this chapter will focus on the analysis of informed consent, its requirements, the factors that may affect the process, and the validity of the consent. Furthermore, the chapter will focus on the issue of who should provide the consent for the individual and the role of community consent in the assurance of procedural fairness.

Informed consent:

Informed consent was conceptualised in western countries and instated through the Nuremberg Code in the wake of the Nazi camp experiments to reinforce the importance of an individual's right to protect oneself from harm (Nuremberg, 1949). Since the publication of the Belmont report, informed consent along with REC review formed the primary protectors of the welfare of the potential research participants (Institute of Medicine, 2002). Literature refers to two different meanings of informed consent (Beauchamp and Childress, 2009: 119). The first one focuses on informed consent from an autonomous decision making perspective. It as a way for people to express their autonomy and right to decide what should and should not be done to their bodies. The purpose of informed consent is to ensure that the potential participants decide whether they become enrolled into a clinical trial or to refuse being enrolled. At the same time it means they also retain the freedom to withdraw from the research at will with no penalties or retributions (Emanuel et al., 2000). Informed consent may be defined as the translation of a person's autonomy. However, limiting the definition of informed consent to a person's autonomy means many other essential factors

that feed into informed consent go amiss such as the allowance of others to perform actions that otherwise may not be permitted. In general, one solicits consent from an individual before initiating the interaction with them regardless of whether this interaction is harmful or beneficial.

The second meaning of informed consent refers to the social rules of consent which does not see informed consent as an autonomous act; but sees it through the social rules of informed consent. Hence if the agreement of an individual cannot be defined as an informed consent within certain social boundaries, it cannot be given the title of informed consent but can be considered as an authorization for a certain action to be taken. Beauchamp and Childress provide an example of a mature minor to clarify this meaning of informed consent (Beauchamp and Childress, 2009: 119). Although mature minors may provide their agreement for a certain procedure or intervention, this agreement cannot legally be termed informed consent. Hence their agreement is referred to as an authorization by that individual for a specific procedure or intervention to be performed. This second meaning of informed consent will be discussed later on in the chapter when considering community consent.

Informed consent is an essential requirement within clinical trials. As the name implies, the agreement of the potential participants has two parts. The first part is reflected in the term “informed”. The person requested to agree to participate requires a certain amount of information to make a balanced, informed decision. This provision of information is generally considered the responsibility of the research teams. Yet, simple provision of information assumes that the receiver easily understands and processes the content of the information being presented and rationally states a preference. This is not the case in reality. Researchers

are obligated to give as much information to the potential participants as they want or need to aid them in making the most suitable decisions for themselves.

The second part of the term “informed consent” is “consent” or the agreement given by the potential participant. However to say that these are the only two requirements for the agreement of the potential participant and to assume that each and every potential participant requires exactly the same amount of information cannot be further from reality. Multiple other factors play a role in a person's decision making process including how they process the information presented to them and how they evaluate the benefits and harms attached with the interaction. Participant relevant issues which may influence this processing of information may include for example, the potential participant’s level of education, the availability of other options to choose from, future plans, and personal beliefs. However, all these factors that influence the decisions made by potential participants exist worldwide and are not specific to developing countries. However, given the surrounding circumstances of potential participants within developing countries, these factors may have greater influence on the potential participants being recruited from these regions. The levels of education are generally lower within some developing countries than industrialized countries. Furthermore, the beliefs about the causation of illness may differ from those held by potential participants residing within developed countries. All these factors will be discussed in more detail later on in this chapter.

Requirements of informed consent:

The purpose of informed consent is to ensure that the potential participants decide whether they want to become enrolled into a clinical trial and also retain the freedom to withdraw

from the research at will with no penalties or retributions (Emanuel et al., 2000). This means that the potential participants exercise their autonomy. More recently, some individuals have proposed that informed consent should provide a way for potential participants to waive certain ethical and legal norms for the purpose of allowing invasive research (or medical) interventions (Manson and O'Neill, 2007). Otherwise stated, by giving informed consent an individual permits researchers to do things to his or her body which may not otherwise be allowed outside the scope of the research, either ethically or legally. In this situation, the trial participants suspend their right to be treated with a known proven medical intervention, while the researcher gains freedom to conduct the trial without fear of legal or ethical repercussions. Whichever way we view informed consent, certain requirements have to be fulfilled before we can label the agreement of the individual potential participants' as an informed one and for the interaction to be labelled as a procedurally fair one. At the most basic level, these include three elements: Information, comprehension, and voluntariness (Belmont, 1979). Other elements are favored by the medical, philosophical, and psychological literature and include competence, disclosure, understanding, voluntariness, and consent. (Beauchamp and Childress, 2009: 120). The next section will simply present these five requirements. This will be followed by an in-depth analysis as to why these requirements do not reflect the spirit of the whole process.

1. Competence:

The basic meaning of the word competence is the ability to perform a given task. This ability to perform may vary from situation to situation. For example a person may be competent in making financial decisions, but may be incompetent in making medical decisions. Hence

incompetence is limited to the area where the person is incapable of making decisions. Furthermore, competency may vary from time to time. So a person incapable of making competent decisions at a given period in time may be fully competent at a later time to make decisions regarding the same issue. This is because competence can be affected by so many factors for example illnesses whether physical or psychological, or medications. Therefore, generalizations about competency cannot and should not be made either within clinical practice or within clinical trials. Yet in order for a person to make a competent decision, they need to understand the information being presented to them, be able to reflect on them, understand the consequences of their decisions, and then give their consent. Although there are tools and testing methods to assess the competence of individuals, they will not be discussed further here. Still the assessment of level of competence of potential participants is not routinely done unless there are reasons to lead the researchers to question the level of competence. If this is done it should not be because the potential participants are from developing countries but because the individual potential participant displays signs of lack of competence.

2. Disclosure:

Before reaching a decision regarding any given trial proposal, and to aid them in their decision making process, potential participants need to become reasonably knowledgeable about the research proposal. The researchers and their teams hold the responsibility of disclosing informing the potential participants about certain aspects of the research. This process is aimed at helping the potential participants to make choices that fit in with their future plans, goals and values, and evaluate the acceptability of the risks and benefits of the

proposed trial. The disclosure of information helps participants to better understand what is being asked of them so that they may reach a decision whether to accept being enrolled into the trial or to decline the offer. Hence the researchers/sponsors hold the responsibility of disclosing certain information to the potential participants. This information typically includes the purpose and duration of participation, procedures to be used, reasonably foreseeable risks, expected benefits to participant and or society, alternatives to participating in research, as well as others information that the potential participants need to know about (Sales and Folkman, 2000).

However, through focusing on how much information to disclose in order for the level of understanding of the potential participants to increase, the essence of the process itself and the meaning of informed consent became distorted. More information needed to be disclosed to the potential participants due to the increasing complexity of medicine and science and the procedures used within the trials. The issues of focus became risk management, legal protections of sponsors, and adherence to federal regulations (Institute of Medicine, 2002: 121). It was assumed that each and every possible potential harm should be disclosed to the potential participants in order for any future complaints made by the participants to be covered by the argument that these harms were disclosed and the decision of the participant was informed. Although undoubtedly, information is an important factor in the “informed consent” process, we still need to assess whether this approach of full disclosure is correct and more importantly achieves the ethical requirement of “informed consent”. Then it has to be decided exactly how much information should be disclosed to the potential participants.

There are different views on how much information should be disclosed to the potential participants. A minimal standard approach may be used where an absolute minimum amount of information is disclosed to the potential participants regardless of any other factors that may influence the consent process. The problems with this approach can be seen on two levels. The first level is that even the minimum required information can be too much information. The minimum disclosed information mentioned by Sales and Folkman can be perceived by some potential participants as being “too much” information especially if given at once (Sales and Folkman, 2000).

At another level the problem with the minimum approach is the difficulty in sustaining this level of disclosure by the researchers or their teams. The difficulty in the sustainability of this approach is that certain individual potential participants may require more information in order for them to make an informed decision. They simply cannot make a decision regarding their enrolment into the trial with the limited amount of information provided to them by the researchers/sponsors. In these cases giving participants minimal access to information does not work or seem fair. Requiring researchers to grant participants a standard kind of disclosure does not, as Manson and O'Neill state: "ensure that the epistemic norms of successful communication are met" (Manson and O'Neill, 2007: 90). Furthermore, there is no agreement as to what exactly constitutes minimum required information.

The other approach which the researchers and their teams could apply regarding the disclosure of information to potential participants is the full disclosure approach. Here the researchers and their teams tell the potential participants about each and every single detail within the trial proposal. This approach however also fails in ensuring that “informed”

consent is given by the potential participants. Giving too much information to potential participants could hamper their understanding rather than improve it (Jansen, 2014: 31).

"As you keep on explaining, you come to a point where they get lost.

The major areas dissolve out of their mind they might follow you at first but as you keep going, you lose them if you talk for five whole minutes you will lose them." (Molyneux et al., 2004: 2555)

Both of these approaches fail to ensure that the "informed" part of consent is incorporated into the agreement given by the potential participants. One study has shown that both potential participants and researchers place little weight on the value of informed consent anyway (Lidz et al., 1983). They see it as a form to be signed by the potential participants. The main purpose for its existence was dismissed by both the participants and the researchers. Furthermore, the method of presentation of the required information to the potential participants is also problematic. Studies have shown that the researchers themselves focus on certain information and tend to dismiss others. For example, Cousino and colleagues found that the information being emphasized within a phase I paediatric research included drug safety, dose findings, and dose escalation (Cousino, 2012).

There are three different standards of disclosure which have been considered from both a legal and an ethical perspective. Each will be presented separately (Beauchamp and Childress, 2009: 122).

2.1 The professional practice standard:

This standard of disclosure considers that the amount of information to be disclosed to the patient or potential participant should be left to the discretion of the health care provider or the researcher. This is based on the concept that just like the best amount of information to be disclosed to a patient should be left to the health care providers, the amount of information to be disclosed to the potential participants should be decided by the researchers since they are responsible for maintaining the best interest of the participants throughout the trial. The problem with this approach is that it fails to realise that in so many situations whether within clinical settings or research settings there are often no standards for disclosure of information. There is no agreed upon amount of information that has to be disclosed before we can say that proper disclosure has been done. In addition, it cannot be ignored that certain health care providers or researchers failed to communicate properly with their patients or potential participants or may present them with inaccurate or false information. Furthermore, the approach relies purely on the reasonable character of the person in charge of disclosure and tends to forget that the final decision lies in the hands of the patients and the potential participants.

2.2 The reasonable person standard:

This approach to disclosure requires health care providers and researchers to disclose information based on what a reasonable person would need to make a decision. The amount and kind of information needs to be disclosed by the researchers based on the researcher's estimation of what a "reasonable person" would want to know. The problem with this approach is that there is no clear definition of what a "reasonable person" is. Therefore,

researchers need to depend on this hypothetical so called reasonable person in order to assess the information to be disclosed. The other issue with this approach is that studies have shown that 12% of people surveyed stated that they did not use the information provided to them by the researchers while making their decision (Beauchamp and Childress, 2009: 123).

2.3 The subjective standard

This approach to disclosure requires researchers to disclose information to potential participant based on the informational needs of the potential participants. This standard is built on the concept that individuals needs for information differ, they relate to their past experiences, beliefs, and future plans. The down side to this approach is that the person providing the information needs to be knowledgeable about the needs of the person receiving the information. Hence the researchers need to be aware about the potential participant's past history and beliefs for example. This is very difficult to apply in clinical trials given that the researchers do not know much about their potential participants. Still it is a much better approach than a standard disclosure based on the researcher's or the reasonable person's needs. Researchers could adapt this approach but with some changes. Instead of basing their tailored approach on their knowledge of the potential participants as physicians do with their patients, they could tailor their level of disclosure based on the questions being raised by the potential participants. This is perhaps the best approach to ensure that the level of disclosure is tailored towards the potential participant's needs instead of adopting a rigid maximum or minimum approach.

Commitment:

Another important point which needs to be stressed during the presentation of information to the potential participants is the commitment expected from them. This is the last requirement that Manson and O'Neill talk about, and that is the commitment that has to exist within the anticipated researcher-participant relationship.

The researcher's commitment comes through their assurance and maintenance of the standards of their practice, maintenance of the best interests of their potential participants, and their action in accordance with their trial proposal. This commitment however can only become real when potential participants consent to their enrolment into the trial. Therefore, the researcher cannot commit for example to maintain the best interest of a potential participant who either does not agree to enrol into the trial or is excluded from the trial for other reasons.

On the other hand potential participants are also believed to have certain commitments they have to meet prior to their enrolment into the trial. The first commitment expected from the potential participants is their understanding of the information presented to them by the researchers and their teams. The agreement of the potential participants to be enrolled into the trial has to be based on their understanding of the relevant details of the trial proposal. According to Manson and O'Neil's opinion, potential participants cannot agree to be enrolled into the trial, if they base their decisions on misunderstandings, if they misunderstand the proposal, or if they convey their decision in an unintelligible way (Manson and O'Neill, 2007: 93). This failure comes about even if the researchers meet their requirements and provide the essential required information. Potential participants are expected to agree to be

enrolled into the trial only if and when they understand the information being presented to them. Since this issue relates to comprehension and how it is assessed, this point will be discussed in more detail in the next section.

Another commitment expected from the potential participants when enrolling into a trial according to Manson and O'Neill which relate to consent is that the potential participants should give their consent once they perceive that the researchers intend no malice towards them through harmful or wrongful actions. By communicating a decision to the researchers, the participants waive their ethical and legal rights not to have certain things done to them, provided the individuals concerned have understood the information presented. Someone who consents to being enrolled in a trial cannot later on claim that their enrolment itself into the trial or the investigations carried out as expressed in the trial proposal caused the harm. This consideration of harm does not include actual harms which may be unanticipated and inflicted upon the trial participants during the course of the trial. Furthermore, the potential participants have a commitment to follow through with their consent. They agree to participate in the given trial throughout its duration which they are informed about and they have to be committed to that agreement. Trial participants should not change their mind during the course of the trial and decide to withdraw from the trial for no obvious reasons. If participants were given this total freedom of withdrawal, and big numbers of participants decided to withdraw from the trial, then researchers/sponsors may find that these withdrawals affect the trial results leaving the results unreliable and un-generalizable. It is important to emphasise here that this limitation of withdrawal does not include all participants under all circumstances as this will go against the principles of voluntariness and

informed consent. What is being called for is that participants' withdrawals should be justified by rational reasons only. Furthermore, the withdrawal of participant data once analyses, especially if it will affect the trial results may not be guaranteed as well especially if the data has been anonymized. This ensures that there is commitment from both sides involved in the agreement. Both parties involved in the research have commitments, the researchers as well as the potential participants.

Information sheets:

Another issue which is related to disclosure is information sheets which are used as a method of conveying information to the potential participants. Anyone who has had to deal with information sheets knows that the average person finds these sheets complicated and difficult to understand. This problem occurs frequently in developed country settings (Joffe et al., 2001; Mason and Allmark, 2000). Research which has focused on informed consent has found that they are, in general, "too high to achieve broad comprehension" (Institute of Medicine, 2002: 126; Briguglio et al., 1995; Grossman et al., 1994; Hochhauser, 1997). When considering developing countries and the issue of information sheets, other issues emerge including the amount of information contained within the consent forms, the language used, and the beliefs people in developing countries hold towards causality of disease (Lynoe et al., 2001).

Typically all the required information is given in the information sheet. These documents were adopted because of a need to protect potential participants from abuse or coercion and to prevent their participation in something against their will. The need to protect potential participants from developing countries from coercion is just as important, if not more

important, to emphasize as in industrialized countries. Because of all the negative circumstances surrounding people in these countries ranging from political regimes to grave poverty, accompanied by the need to instil better healthcare services in communities there, researchers should ensure that the potential participants being approached act freely and willingly when deciding to participate in a trial. Hawkins certainly agrees with this, she states:

"even if informed consent is a Western practice reflecting Western values, it is worth remembering that RCTs are also a Western practice that reflect Western values.....It would not be surprising to discover that a community with no tradition of research will have had no prior need to develop a practice of individual consent. But it would be too hasty to assume that it would not benefit from having a practice such as informed consent in place when it begins to participate in research."

(Hawkins and Emanuel, 2008: 27)

First of all, information sheets are generally very long, often exceeding twelve pages (Creed-Kanashiro et al., 2005: 926). This issue does not reside only within developing countries. In fact, problems associated with lengthy information sheets also surface in developed countries. Overly long forms tie into the sponsor's emphasis on covering all the legal aspects (Flory and Emanuel, 2004). Whereas the focus of these documents should be the moral aspect of the informed consent process and how to simplify the information to the potential participants in order for them to make an enlightened decision. It should be ensured, usually by the REC, that information sheets do not overwhelm participants with confusing

information and that the document contains wording that is understandable and clear to the intended reader. Therefore, researchers and their teams should draft substantially shorter versions of these documents.

Secondly, information sheets are usually written up in industrialized countries meaning that the research teams must first translate the document into the local language before potential participants can be expected to understand the information given to them and make an informed decision. Although the researchers are responsible for providing a translated informed consent form, the REC holds the responsibility of verifying that an accurate translation has occurred. Therefore, some argue that the REC within the host country should draft the documents for a particular trial because the REC members know better how to relate research information to the population concerned in an appropriate language and in a simple form. Adopting this practice of course may not meet standards set by the developed countries or receive approval from the trial sponsor because of the legal value of these documents in developed countries.

The researchers may have to resort to local translation offices and deal with inevitable problems arising from literal translation whereby the essence of the information does not necessarily get properly reflected in the final document. As a result, the potential participants may miss some of the essential information deemed important for their understanding of the research. Asking an expert from the industrialised country or someone from the research team in the developing country where the trial will be performed to review the translation may resolve the problem. Another recommendation aimed at reducing the risk of losing meaningful information involves the translation of the documents initially

from English to the other language and then back to English again. Any misrepresented, inaccurate, or totally missed information should become apparent in the final translation.

Furthermore, the potential participant should receive all the essential information verbally and in writing (and perhaps in other forms like video tapes, if available) in a language that is easily understood by a lay person or a non-scientifically oriented person.

3. Understanding:

The next step in the informed consent process is the assessment of the level of understanding of the potential participants. Studies have shown that potential participant understanding of the information presented to them varies considerably. For example one study showed that despite the fact that the potential participants stated that they were happy about the informed consent process, three fourths of the participants did not know what unproven intervention means while one fourth of the participants thought that the purpose of the trial was to benefit them directly and not future patients or populations (Joffe et al., 2001). How well participants understand the information presented to them by the researchers or their team is influenced by many factors. Before analysing the factors that may affect the understanding of the potential participants, we have to specify exactly what level of participant understanding should be accepted by the researchers and their teams. In extreme situations, the highest level of understanding could be required where potential participants are required to understand every single detail about the trial and its processes. However in such cases, the goal itself may not be realistically attainable. No single potential participant will completely understand each and every aspect of the proposed trial. If this approach is acquired, the researchers/sponsors may face extreme difficulty in recruiting the

required number of participants not because none of them understand the trial proposal but because the threshold of level of understating has been set too high to be achieved. This also means that large numbers of potential participants may be excluded from the trial for that same reason.

Alternatively, lower levels of potential participant understanding may be acceptable. Hence the question we need to answer is: Can we accept enrolling potential participants who understand only part of the proposal, or understand the general essence of the proposal but who still fail to grasp certain aspects of it? People make choices and understand information from subjective bearings based on so many factors such as their values, future plans, and mindsets at the time of decision making. As long as the potential participants understand that they agree to participate in research rather than see the trial as an offer of treatment, recognise their right to accept or refuse participation, and know the kind and level of risk involved, then assessing the level of understanding becomes the responsibility of the individual participant.

Getting key messages across to a participant demands proper communication between individuals involved rather than the simple telling of certain information. Disclosure without further focus on the needs of the potential participant assumes that the recipient of the information takes in and understands all that is presented, which is not always the case. The level of understanding of information varies from one person to another due to several factors that may have direct relevance to a potential participant such as his or her beliefs, anxiety, ignorance about certain facts, or lack of knowledge of the consequences of certain actions. External factors affecting the level of understanding might include for example

ambiguities in the use of terminology where certain terms can be applied in different situations with different meanings, or interpersonal distinctions exist in the way terms are interpreted e.g. the term randomization. Therefore, different people will receive the same information in different ways. Some of the factors thought to influence a person's comprehension include his or her rationality, level of education, and beliefs regarding the causation of illness. Each of these factors will be discussed in further detail below.

3.1 Rationality:

Rationality is the possession or utilization of reason or logic to analyse information and reach a decision about a specific situation. However, rationality occupies a much broader space than logic. Logic is the process of reasoning. It is "concerned with analysing the patterns of reasoning by which a conclusion is properly drawn from a set of premises, without reference to meaning or context" (Collins English Dictionary, 2003). Rationality, on the other hand, includes other aspects such as past experiences, beliefs, and expectations. According to Sanford Encyclopaedia of philosophy, rationality is: "the general human capacity for resolving, through reflection, the question of what to do" (Sanford Encyclopaedia of Philosophy). Humans can only make rational decisions that fit in with their own personal values and future plans and can visualize how a scenario will play out for them only when given sufficient information about the situation in the first place (Verastegui, 2006). However, rationality does not depend on information entirely in each and every situation. Rationality entails assessing the best outcome based on the circumstances and situations surrounding a person. Therefore, a person can make a rational decision without possessing a

lot of information. Acquiring information is just one of the aspects needed to make a rational choice (Savulescu and Momeyer, 1997). Other factors that come into play in reaching a rational decision include entering into a rational argument and having rational beliefs.

The rationality behind any given decision is not judged by agreement or disagreement with the presenter of the information. The refusal or acceptance to participate also does not justify placing the rationality of that person under suspicion. The rationality of the decision is based on the person's perspective of what he or she believes is good for himself or herself according to a number of factors outside the information provided by researchers. These factors may include employment, future plans, and family circumstances. Respecting a person's choice or autonomy includes the respect for his or her decision which may seem irrational to another but makes perfect sense to the person making that choice.

In developed and developing countries alike, people of adult age with full decision making capacity may be assumed rational except when certain conditions apply that reduce the individual's decisional capacity such as an illness affecting cognitive abilities. Therefore, if people in developing countries are assumed rational, then they will make rational decisions dependent on receiving appropriate information and their personal values and future plans, among other factors.

3.2 Level of Education:

It is assumed that the higher the level of education possessed by an individual, the easier it may be for the researcher to achieve good communication with that person and consequently, the more likely he or she will understand and process the information being presented. I do not believe that a higher level of education guarantees better

comprehension, nor does illiteracy mean a lower level of comprehension. Issuing a blanket statement suggesting all populations in developing countries are poorly educated has no foundation. The problems faced by the researchers in developed countries regarding the comprehension level of potential participants may parallel those within developing countries if we consider only level of education and the way it affects command of knowledge. Admittedly, a potential participant with a higher level of education may have a broader level of knowledge and may understand some of the concepts of the trial more easily than the potential participant with a lower level of education. However, this does not lead us to conclude that the latter does not understand the information or that his or her level of understanding will not increase when proper explanation is performed by the researchers or their team. In such cases what is required from the research team is a simplified provision of the information and more tailored sessions to ensure that the potential participants understand the information and the basic concepts of the trial. Hence, from the point of view of an individual's comprehension, a low level of education although perhaps influential, does not necessarily hinder understanding of the material presented. It only means that in this case, the researchers and their team need to put in an extra effort to ensure better communication with potential participants by providing the information in a simple understandable fashion.

3.3 Beliefs about causation of illness:

Some people in developing countries maintain nonconventional beliefs about the causes of illness and methods of treatment. They may believe for example that traditional interventions are more effective than medical interventions or pharmaceutical agents. Some

populations see illness as evil work caused by spells or magic (Carteret, 2008). One can clearly see how this kind of belief system can affect informed consent and the understanding of information presented to potential participants. In such cases the researcher may have a harder time explaining the purpose and goal of the research to the potential participants (Truog et al., 1999: 149). It has to be stated though that the existence of these beliefs does not mean that the potential participants will not understand what is being presented. Rather it implies the need for a more comprehensive approach by the researchers and their team to ensure that the information is understood by the potential participants.

Another potentially complicating issue which links to the beliefs of the potential participants, and relates to the health care system existing within those countries, is the perception of the role of the health care providers and the interaction between the members of the public with the health care providers within developing countries. People living in developing countries see contact with a health care provider as an opportunity for treatment. The concept of interacting with the health care provider, in the role of a researcher, with the aim of being recruited into a trial does not exist. The idea of research does not enter into their culture. The members of the public see the interaction with the health care providers as an opportunity for receiving treatments. They do not perceive that a health care provider may take on another role which may not provide direct benefit to the individual person. This point will be discussed in more detail later on in chapter four when discussing the confusion between the physician-patient relationship and the researcher-participant relationship. Still the understanding of the potential participants cannot be said to remain stagnant. It may be improved through the efforts of the researchers and their team. How much information they

provide, and how much effort they put into its simplification and the assurance of understanding of the potential participants has a major impact on the level of understanding of the potential participants.

4. Voluntariness:

Voluntariness is generally evaluated in the context of the presence of adequate knowledge, absence of psychological compulsion, and absence of external constraints (Feinberg, 1973: 48). However, Beauchamp and Childress only consider external constraints in their analysis (Beauchamp and Childress, 2009: 132). Through this focus on external constraints of factors that may have an impact on the voluntariness of the decision made by the potential participants three have the most influence. These include deception, coercion, and persuasion.

Deception and manipulation:

In some circumstances the researcher/sponsors may decide not to disclose all the relevant information because they fear that giving out too much information may frighten the potential participants and lead them to decide not to take part in the trial. This leads the researchers/sponsors to withhold certain information in order to encourage participants to accept being enrolled into the trial. This sometimes occurs when the clinical trial is complicated and contains too many technical steps. Therefore, the team avoids under-recruiting by concealing some information which may actually influence a participant's choice. This act is also known as manipulation: to adapt or change something to suit one's purpose or advantage (Free dictionary). This argument of withholding certain information

from potential participants for fear of under-recruitment is not supported by evidence from the literature. Furthermore, by performing such an action and by leading the potential participants to make certain choices, the voluntariness of the decisions made by the potential participants is questioned but not its rationality. The potential participants made certain choices based on the information being presented to them. Although these decisions may be rational, the simple fact that the potential participants may make different choices if they had access to further information means that the choices made under manipulation and deception are not voluntary ones and hence fail from a procedural fairness perspective.

Coercion:

Coercion means to compel someone to act against his will by intimidation or threats (Freed dictionary). According to Hawkins and Emanuel, coercion has two elements. The first is the set of options available and the second is the interference by others (Hawkins and Emanuel, 2008: 25). It is perhaps the second element which is more important within the interaction between the researcher/sponsors and the potential participants. Do the researchers interfere with the choices made by the individuals, threaten them, or intimidate them in order to make them agree to participate in a trial? Although one could make up a scenario where the researcher intimidates the potential participants into participation by mentioning that they would become worse off if they refuse to enrol, this does not take place in reality. The researchers have no input or influence on the existing conditions within developing countries, they do however present offers to the potential participants who under the existing circumstances may see them as very attractive and irresistible. However, it does not mean that the researchers/sponsors coerce the participants by simply offering them a

chance to improve their situation. Even when someone's available choices are narrowed significantly he or she may still reach an informed voluntary decision based on the limited information available at the time the decision is made.

Persuasion:

Persuasion is the change of a person's belief through the influence of another's arguments. The influence that occurs has to be done through the use of reason rather than emotions. Although in the majority of interactions between the potential participants and the researchers, the arguments presented by the researcher and their teams would have an impact on the opinions of the potential participants, the problem with this point is that its results may be inconsistent especially within issues related to health care. Where a certain argument may have a positive impact on a particular potential participant's opinion, the same argument may hinder the decision making process when presented to another potential participant.

Having presented the factors that may influence the voluntariness of any given potential participant; we need to now focus on the issues of whether populations of developing countries can act voluntarily or not. The governments in many developing countries have very limited resources and this is reflected most obviously in the kind of services provided for the populations within those regions. Health care is often one of the areas showing shortages of resource. Many of the basic medical therapies for conditions that affect the population do not exist or there are very few available options.

The health care systems existing within developing countries lead us to wonder if people who agree to participate in clinical trials do so because they want to help their community, or because it is the only way they can get any kind of health care services. Desperately ill people who have no hope of receiving any kind of treatment from their own government will seek any opportunity for help, which brings the issue of voluntariness into the discussion. To know whether individuals within developing countries are capable of making voluntary decision we need to first look at the concept of vulnerability and proceed from there. In a broad sense vulnerability means:

"Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests." (CIOMS, 2002: 44)

So, by definition, people in developing countries are likely to be defined as vulnerable. They have less power than the researchers/sponsors coming from the west and face shortages of basic health care services. Therefore, it is perhaps more appropriate to question why researchers choose vulnerable populations in the first place. Researchers usually carry out studies anywhere and enrol their populations with the aim of benefiting that specific population. They seek to find a treatment option that best suits the population concerned. A clinical trial aspiring to help people in developing countries must recruit its participants from that particular setting because the research population has to represent the people destined

to benefit from the results; i.e. the participants will have to come from what are termed vulnerable populations.

Assuming this to be the case then we need to assess whether vulnerable people can make a voluntary choice. Indeed many argue that vulnerable people cannot provide voluntary consent because of their specific circumstances. Emmanuel presents one such argument:

"You can tell a person [in a poor developing country] that this is research, but they hear that they have a chance to get health care. How can you put them in that position and then say they are giving informed consent?" (Emmanuel et al., 2005: 336)

Emmanuel's quote highlights the absence of voluntariness in these situations. Rothman also argues that:

"Abject poverty is harsh enough without people having to bear the additional burdens of serving as research subjects." (Rothman, 2000: 92)

I would argue differently. Having many choices or fewer alternatives to choose from does not define the voluntariness of a given decision. Although a difference exists between having no treatment option and having few options to choose from makes the person's decision easier to reach, potential participants can still make informed voluntary choices despite these restrictions. The first scenario where few alternative interventions exist somehow parallels the situation in other countries and is not peculiar to developing countries. Potential participants invited to take part in a trial can make a choice regardless of whether the

treatment is superior to the existing alternative. If we assume that a state of equipoise exists, then even the researchers do not know the outcome of the trial. What the potential participants are asked to do is the acceptance to be enrolled into a trial to prove the effectiveness or superiority of the new intervention in comparison with existing ones. Hence the issue is not whether many, or few, options are available outside the scope of the trial. The issue is about the freedom of choice made by these potential participants. Many people have had to make health related decisions or choices when few options existed for them. Pace argues along these same lines. She argues that many of us have had to make a choice at some point in our life where our options were restricted. She states:

"We have all made decisions when we felt our choices were constrained or defined by the situation or the needs of those surrounding us, and yet we could still make a voluntary choice." (Pace and Emanuel, 2005: 12)

I agree with Pace and believe that there is a difference between having constrained choices and being coerced or forced to do something we do not want to do. Most importantly, a potential participant makes a choice that is free from any external pressures, coercion, or deception. Therefore, decisions made in the absence of these external factors can be assumed to be fair at least from a procedural perspective.

The second scenario, where no treatment options are available to the population, raises more concerns. People in developing countries without existing treatments who are approached by researchers asking for their consent to participate in a trial may perceive

volunteering as the only way to get treatment for their illness. For many desperate individuals enrolling seems like a better option than refusing to participate when no other treatment alternatives exist. These potential participants agree to be enrolled into the trial despite the chance of them being allocated in the placebo arm of the trial. They enrol in the study with the hope of receiving therapy and being placed in the active arm of the trial. In reality, however, this hope of being placed within the active arm of the trial may also be a hidden wish of potential participants within developed countries as well. Emanuel seems to think that because people in some developing countries have no access to health care services that they are simply incapable of giving informed consent. However, Emanuel's argument is mistaken. Although his views may apply to some potential participants, it cannot be generalised to all populations. It cannot be assumed that all poor people lack the capacity to give voluntary informed consent because of deficiencies in health care services. Taking this stance would leave a large proportion of potential participants out of the equation, even those within the developed part of the world. To prove the wrongness of the link between the lack of options and the voluntariness of the choices made by potential participants, a parallel scenario from a clinical situation will be presented. Within some medical conditions, only one treatment option may be available for the patient. This treatment option may or may not carry a high risk of failure or complications. In such cases the patient's decision to accept this single option cannot be defined as involuntary provided that enough information has been provided to the patient and the choice was reached without external forces. In such cases it would be difficult to argue that the decision made by the patient is an involuntary one. If we did, then we would be arguing that voluntary consent can only be achieved if

several options are available to choose from. This would be a very difficult argument to defend not to mention the unrealistic approach it is taking. The reality of the matter is that even when we say that only one option exists, we are forgetting that the alternative is refusing that option. The patient may still choose not to go ahead with the treatment option. The same argument applies to clinical trials. Even if no options of treatment exist outside the scope of the trial, the potential participants' decisions cannot be defined as involuntary blindly and for the simple reason of the in-availability of further options. These potential participants may still refuse to participate in the trial. Participants in developing countries are desperate for treatment. Agreeing to participate in the research by giving consent gives these people some hope of improving their situation. As Hawkins points out:

"Given the non-ideal background conditions under which people find themselves, there should be a very strong presumption in favour of the principles that would allow people to improve their situation if they give appropriately robust consent, if doing so has no negative effects on others." (Hawkins and Emanuel, 2008: 84)

Using Hawkins point of view to contradict Rothman's earlier arguments opens the question: because of the abject poverty that people in developing countries suffer from, is it fair to deny them access to what may be the only chance they have at improving their circumstances and receiving the benefits of a clinical trial? According to Hawkins, the unfairness lies in denying potential participants the potential benefits of the trials and not the other way around. Despite the harsh circumstances surrounding vulnerable populations,

these people can still reason and assess their options. Participating in research may be the only perceived route for receiving any kind of treatment even if given for only a short period of time, and the person may still make an informed voluntary choice in this case. Furthermore, if the trial itself is intended for the benefit of these vulnerable populations, there is no alternative but to recruit them as participants into the trial. The best approach would be the assurance of their understanding of the information being presented to them and the nature of the trial. We all face difficult situations in which we have to make choices. This does not mean that we reach our decisions involuntarily.

Citizens of developing countries become regarded as vulnerable when their situation deprives them of so many basic services taken for granted by people living in the developed world; yet implying that it is better not to let these people choose freely whether to enrol in a study that might benefit them, or harm them in some cases, is difficult to justify. Rather increasing the available options gives people more space to exercise their right to choose or their autonomy. Vulnerable people can make a voluntary decision even when only a few choices or one choice exist.

Perhaps a larger obstacle to the voluntariness of the decisions made by the potential participants is the nature of physician-patient relationships existing in developing countries. The way this relationship is perceived within developing countries may present a bigger stumbling block for researchers. The relationship between the patient and the health care provider within some developing countries health care setting still takes on a paternalistic tone. The necessity to get informed consent does not exist in some developing countries. People in these countries still view the health care provider as an all knowing individual and

rarely question the decisions made by their doctors. In fact it is considered inappropriate to question a doctor (Molyneux et al, 2004: 2551). Other factors which prevent people from asking question include trust and fear of the health care providers (Molyneux et al, 2004: 2553). Cases where consent is taken and grounded by patient signing a form may hardly classify as an informed decision. Such individuals receive very little or no information; they are given the form to sign and that is it. No questions are asked and certainly no information is volunteered from the health care provider. The potential participants feel it inappropriate to question health care providers and fear repercussions from doing so such as abandonment and termination of treatment. This barrier may be hard to break down and voluntariness sustained when the potential participants view the researcher or health care provider as the one who knows best.

5. Consent:

The next step in obtaining informed consent is the signing of the informed consent form. Once the participants understand the information at a level acceptable to them, and the researchers and their teams are satisfied that the potential participants understand the information presented to them, the potential participants then grant the researchers permission to enrol them into the trial. Usually, a written form of consent is taken, an approach particularly applied by sponsors from developed countries that worry about the legal more than ethical requirements of the consent process. Another study showed that one out of seven participants admitted they did not even read the consent form before signing it (Getz and Borfritz, 2002). Hence the same arguments made about information sheets and how shorter versions should be drafted and the assurance that the essential information

existing within the document, or its essence, does not get lost during the translation also hold for the consent forms. Also, studies have shown that potential participants find consent forms containing tables and more white spaces easier to understand (Sales and Folkman, 2000). However, the circumstances in developing countries make adopting an “in writing only” approach to consent difficult. People in developing countries who are living under the rule of oppressive regimes may see signing a form, especially in a language they do not understand, as a threat. Some individuals may have lost some important property such as land or a house in the past as a result of signing a form (Creed-Kanashiro et al., 2005). So even if these individuals accept being enrolled in a trial, asking them to sign a form may actually cause them to change their minds and to refuse to be enrolled into the trial. But do we really need to impose such strict rules? Does informed consent mean only written consent? The written type of informed consent may serve well enough for those individuals who have no objection to signing the informed consent form. However, other options may be made available for those who feel uncomfortable with signing documents. I believe that other ways of proving that the individual gave his or her voluntary informed consent can be just as effective. In some cases, an individual may consent verbally instead of in writing, forms of ensuring this verbal consent may include videotaping the whole process or audio taping it. Although videotaping represents an unconventional way of obtaining agreement to enrol into a trial, it may help potential participants from developing countries feel less threatened by removing the need to sign a form. Furthermore, videotaping the process of informed consent could reveal the depth of communication undertaken by the researcher/sponsor whereas a written consent does not.

Also, when the review board insists on examining participant consent, video tapes show clear evidence of the individual himself giving the consent, whereas the REC members have no way of knowing whether a signature has been forged on a written consent form. There is no way that the review board would have the resources or the ability to check the authenticity of each and every signature. Therefore videotaping informed consent can be as effective as written consent.

Validity of Consent:

Through the focus on how much information should be disclosed to the potential participants, and the legal requirements of informed consent, the most important ethical essence which is the validity of that consent, was somehow forgotten. To say that the researchers/sponsors' sole responsibility is to disclose information to the potential participants falls short of all that is required from the researchers, their teams, and the sponsors. The issue has to be the assurance that the individual potential participant communicates and deliberates with the researchers. This communication and deliberation process ensures that the concerns of the potential participants and questions receive adequate answers which aid them in reaching an informed valid consent.

The researcher should focus on communication rather than the simple dispensing of information to ensure that participants really understand what they are getting themselves into. I particularly like the argument presented by Manson and O'Neill because it helps us understand the importance of communicating with the potential participants rather than just disclosing a standard type and amount of information to them (Manson and O'Neill, 2007). They suggest that in order for proper communication to take place between the researcher

and the potential participant, both parties should recognise certain obligations. The researchers and their teams must communicate information that is intelligible, and true or honest. Furthermore, the information presented needs to be relevant to the audience (potential participants), and the researchers have to commit themselves to certain actions but only if consent is given by the potential participants.

This approach complements the initial approach to informed consent even if it stems from a different understanding of the need for informed consent. They are basically saying that in order for potential participants to better understand the information presented to them, the researchers and their teams have to target their audience properly. If the information presented is irrelevant to the participants then they will stop listening and consequently misunderstand what is being said to them or refuse to be recruited into the trial. Therefore the trial itself has to be relevant to the potential population in order for the information being presented to be relevant and easily understood by the potential participants. In order to achieve this goal, a tailored approach to communication, rather than disclosure of information, is the most reasonable one. This approach takes into consideration the variations in the needs of the potential participants. In this approach the researchers provide a certain amount of information to all the potential participants including the major procedures, potential risks, benefits, and alternatives in simple forms. At the same time the option of providing further information in greater detail is still made available to the potential participants (Institute of Medicine, 2002: 124). The suggested approach is that the researchers and their teams tailor how much extra information is disclosed and how much more detail and explanation is offered to the potential participants depending on the

participants demand or need for extra information. Individuals who seek further details about the research by asking a lot of question deserve to receive answers to their queries from the researchers or their teams. Yet, potential participants not wanting more information should not be forced to receive further details that may confuse them rather than help them make a decision. This does not mean that their level of understanding of the information provided to them should not be assessed. All it means is that the focus should be on communication and mutual understanding rather than two unilateral actions of disclosure and reception of information (Atkinson, 2000; Coulter, 1999).

“Ideally, the disclosure of information during the informed consent process takes place as a bilateral process involving an exchange of questions and answers between a research participant and research investigator. This interplay is an important and potentially challenging process, as it requires the person obtaining consent to gauge the appropriate level of language and technical detail suitable for the participant’s understanding” (Institute of Medicine, 2002: 124)

Therefore, the real pressure is on the researchers and their teams to present just the right amount of information to each individual to aid him or her in reaching a sound decision. An individual's need for further information may become clearer when the potential participant asks for further details. This approach parallels the approach used in clinical settings where patients have individual requirements for information and further information is provided based on individual needs.

Through this communication process, the information being provided to the potential participants has to be presented in an easily digestible and comprehensible form for the audience at hand i.e. presented in an appropriate language, and given in small bits and in different ways. Providing a lot of information to the potential participants at once may lead to confusion or misunderstanding of the information being presented. Therefore, asking potential participants to read and understand all the information presented to them in one session is an unrealistic request. Participants should be given adequate time to consider whether they want to participate in the trial plus be given more sessions to fully grasp and understand the goals and merits of the trial, its risks and benefits, and how participants are to be divided among the different arms of the trial. This increased interaction between the potential participants and the research team will help ensure that all the concerns of the potential participants are adequately addressed.

Furthermore, only factual information about the trial should be presented. This third point perhaps goes without saying. Only true and honest information should be presented because consent based on false information falls short of being informed, not to mention that it would be classified as being deceptive to the participants. But, what helps convince potential participants that they are being fed true information? The receiver of the information or the potential participant has to assume that the presenter or the researcher is an honest person who is only presenting true claims, unless compelling reasons exist to suspect otherwise. To help in this aspect, the knowledge that an REC has seen, assessed the research, and approved it may also in certain cases, enhance participant trust regarding the truthfulness of the information being presented. Therefore, an element of trust must exist between the

researcher and the potential participant, although this may not come easily given the history of research involving human subjects.

Hence the focus should be on the communications process between the researchers and their teams and the potential participants. To improve this communication and aid the potential participants in reaching a decision that fits in with their plans, goals, and values, we need to understand the factors that may have an impact on this process i.e. factors which may hinder the communications process or improve it.

This is an issue which has been recently presented by Jansen but through a fresh perspective (Jansen, 2014). Although her hypothesis, which relies of the mindset theory, focuses on participants who agree to participate in early phase cancer trials, it could easily be adopted on broader perspective to include other trial participants. She argues that these participants adopt different “mindsets” prior to their agreement to be enrolled into the trial and after their agreement.

The basic concept is that we humans are planning beings and set goals for ourselves. We take on a deliberative approach in order to set our plans and we adjust our actions in order to achieve our goals (Jansen, 2014: 26). The hypothesis builds on the concept that people have two different mindsets which emerge through the “deliberation mindset” and through the “implementation mindset”. It was discovered through the work of Gollwitzer that these two processes use different assessment processes.

“People who ponder a goal decision (i.e. to either pursue Goal A or B, or to pursue either Goal A or stay passive) develop a deliberative mindset that allows them to accurately assess whether a desired

outcome can be controlled by their actions or not, whereas people who are planning the pursuit of a chosen goal develop a mind-set that fosters illusionary optimism with respect to controlling this outcome” (Gollwitzer, 2003: 261)

Hence, people have two different mindsets when going through deliberation and after they have made a decision. Similarly, potential participants have two mindsets. What is interesting is that the processing and perception of information and capability to analyse this information differs between these two mindsets. In the deliberative mindset, potential participants are more capable of receiving information and assessing the risks and benefits of the proposed trial in order to reach a decision. However, in the implementation mindset, potential participants focus on methods of reaching the goal they have selected. Hence at this mindset, potential participants tend to underestimate the levels of risk involved and overestimate the level of benefit not only to future populations but also direct benefit to themselves including the possibility of cure. Therefore, we can say that people are more likely to make accurate estimations about risk and benefit when they are in the “deliberative mindset” rather than the “implementation mindset”. Hence according to Jansen’s hypothesis the researchers and their teams need to ensure that the potential participants are in fact in a deliberative mindset when they are presenting information to them regarding trials where the potential participants are required to make a decision. This has to be ensured so that the potential participants do not underestimate the levels of risk anticipated from the trial, overestimate the levels of expected benefits, nor do they make decisions based on false perception of information which may not necessarily fit in with their plans and goals. In order

to achieve this, researchers and their teams need to ensure that the potential participants are in a deliberative mindset. This is based on the findings of Gollwitzer and colleagues who found that there can be an influence on the mindsets, meaning that they may be induced by asking a person to think about an important aspect in their lives such as their families or their jobs. Their second finding relate to mindsets being generalized across situations. This means that if a person is set into a deliberative mindset in one situation, they will remain within that mindset even if their attention is turned to another unrelated matter. Thirdly they noted that mindsets tend to stabilize over time (Jansen, 2014: 31). The concept is that once individuals enter into a mindset they tend to continue to make decisions within that mindset. Hence researchers may help set their potential participants minds within the deliberative mindset prior to engaging with them in the process of disclosure and requiring them to make a decision. This, according to Jansen can be done by asking potential participants at the beginning of an interaction to think about the process they use when making decisions regarding their families, changing jobs, or buying a car. Once their minds are set within the deliberative mindset, their understanding of the information and their appreciation of the levels of risks and benefits involved would improve.

Still there are factors that relate to the potential participants and which may hinder communications and lead to the misunderstanding of the information being presented to them. These are what Jansen refers to as the “therapeutic error”.

“Patient-subjects enrolled in early-phase cancer trials appear to be making a mistake. They have, or at least appear to have, a distorted

view of their own susceptibility to risks and benefits” (Jansen, 2014: 26)

Although Jansen focuses on early phase cancer patients in her article, these factors may exist within other potential participants including those within developing countries. This therapeutic error may be caused by three different causes: therapeutic misconception, unrealistic optimism, and therapeutic misestimation. Each of these will be discussed separately (Miller and Joffe, 2012; Horng and Grady, 2003).

Therapeutic misconception:

Potential participants often base their decisions of being enrolled into research because they equate the role of the physician with that of the researcher. Potential participants often confuse the physician-patient relationship with the researcher-participant relationship. The misconceptions that surround the roles of the physicians and the researchers create problems. For example, a study which asked participants who agreed to be enrolled into trials for the reasons for their agreement, found out that the most common given reason was therapeutic benefits (Jansen, 2014: 25). Another study by Jenkins et al. found that within meetings held between the researchers and potential participants, the conversation focused on prognosis in 21% of the entire conversation time (Jenkins, 2011). These results reinforce the misconceptions the potential participants may have and emphasise the equation between the roles of the physicians and the researchers. Therefore it is important to clearly differentiate between the physician-patient relationship and the researcher-participant relationship.

Physicians act with the individual patient's best interests at heart; they promote the best intervention for their individual patients because they have a fiduciary relationship with them. They are required to provide the best available intervention to that patient and to advance the individual patient's health according to acceptable medical standards. Through this role, the best interest of the patient should take utmost priority and physicians are held legally as well as morally liable if they fail to place the patient before all other interests, including their own. The same level of fiduciary relationship and rapport does not necessarily apply to the researcher-participant relationship. Researchers are in a moral contractual relationship with the participants and their goal is to answer a scientific question, generate generalizable knowledge, and benefit future patients (Saver, 2009). The individual person's interest is valuable as far as the researcher respects the participants, obtains their informed valid consent, and assures their wellbeing throughout the trial. The provision of treatment to the individual participant for the improvement of their health status is not a direct goal despite the fact that it may come about through the use of the tested intervention or agent or through the more intensified medical follow ups and investigations offered through the trial. Although, researchers are not obliged to give participants proven interventions, the researcher still has the moral duty of keeping the best interest of participants as a priority. This can be achieved by protecting the participants during the trial and reporting adverse events when they occur. Also, they are supposed to compensate trial participants for damages or harms sustained as a direct result of their participation in the trial. Having said that it still stands that researchers still do not have a duty to directly enhance the health of a

single participant since they aim at a much broader scope of interest, namely that of future patients and populations.

The goals of the trial are reached by testing trial interventions on participants and comparing the outcomes with those of other interventions or sometimes with a placebo arm as a means of resolving any uncertainty existing in clinical practice, i.e. equipoise. In many instances, the researchers may also be physicians by profession. This means that some of the participants enrolled into the trial may also be patients of that physician taking on the role of a researcher. This does not necessarily mean that the same duties owed by the physician to the patients are directly transferred to the researcher-participant relationship. It has to be admitted that the researcher/physician may have a difficulty in fulfilling this responsibility attached to his or her different and sometimes competing roles and there may be tension between the two, but this is not our concern here and will not be further elaborated. The focus of the discussion is the duty owed by the researcher to the trial participants. Furthermore it has to be noted that many researchers are not physicians in which case the non-physician researchers become exempt from providing benefits to their participants while physician-researchers are required to provide the proven intervention. This view is problematic since we cannot allow researchers to get away with conduct unpermitted for physicians and vice versa. Regardless of professional status, the researchers should answer their research questions, or at least generate new information that may become useful in the future by ensuring the best interest of the trial participants and giving them their due respect.

Right from outset the physicians and researchers follow two clear and distinct courses of action, but these two paths cross when it comes to interactions with patients or potential participants and their goal to benefit regardless of whether this benefit is directed at the individual patient or collective future patients. The main difference lies in the researcher's and participants' shared knowledge that the benefits of trials are directed at others rather than self. This issue could be overcome if this is stated directly to the potential participants at the time of recruitment. They have to know that they are not receiving treatment for their illness and that they are not being treated. They are merely helping the researchers in generating new knowledge and proving which intervention is more effective than the other. Potential participants agree to enrol into a trial based on information provided to them by the research team, which in part should explain how research seeks to answer a specific question regarding a given intervention. Particular reference should be made to the fact that the treatment of the trial participants is not one of the immediate purposes of the given trial. Admittedly, this understanding may present difficulties especially because of existing health care services within some developing countries, when the participants have no chance of receiving the intervention through other means or access to alternative health care services. Having said that, the external existing factors complicating the relationship should not stop researchers from explaining the trial concepts to the participant nor does it inhibit potential participants from understanding the terms of their participation. Furthermore, the external existing factors do not imply that the physician and researcher assume the same responsibilities.

Therapeutic optimism:

Therapeutic optimism refers to the distorted assumption held by potential participants about the risks and benefit of the trial. Potential participants think that they are more likely than others to benefit from their participation in the trial. At the same time they may underestimate the level of risk involved from the same participation. This relates back to the potential participants being in the implementation mindset and how researchers should ensure that the potential participants are in the deliberative mindset to avoid this downplaying of the risks and over optimism about the direct benefits. Since this has already been presented earlier it will not be discussed further here.

Therapeutic misestimation:

This kind of error on the part of the potential participants refers to their failure to understand the estimated level of risks and benefits. They may have a poor understanding of the probability of risks taking place. This does not relate to the mindset the potential participants are within at the time of deliberation but may be due to simple failure in understanding. This could be more related to the kind of information actually being presented by the researchers and their teams to the potential participants. Hence the problem may be improved through the presentation of the information which should be done in a simple, easily understandable form which is intended to help the potential participants in grasping the chances of risks occurring.

Hence an improved level of understanding whether in developed or developing countries could be achieved and potential participants can develop an improved level of understanding

when exposed to prolonged explanations carried out over a period of time and involving more sessions. This approach gives participants time to properly evaluate relevant information and have their questions answered. Admittedly, applying this course of action takes longer than the analogous process in developed countries; however, it is not a mission impossible. If the researchers and their teams put in enough effort, and present the information in simple language using if necessary and available, different forms of communication such as written documents and video tapes, then the level of understanding of the potential participants should improve, at least with regards to that specific clinical trial. Some researchers have set out to prove this concept. One study which looks specifically at methods aimed at improving understanding of potential participants in developing countries reports the following:

"Our findings indicate that the standard consent process of a single meeting between investigator and volunteers might be insufficient, and that new techniques should be developed to improve the informed consent process." (Fitzgerald et al., 2002: 1301-2)

Another study which solicits opinions of researchers, both from developed and developing countries, who carry out their clinical trials in developing countries and questions how they face the challenge of making participants, understand (Newton and Appiah-Poku, 2007). One of the researchers questioned within this study says:

"If you think they are willing to be part, and they do not understand, then you have to continue the dialogue until both of you are happy

that everything has been understood." (Newton and Appiah-Poku, 2007: 152)

Another researcher within that same study states:

"I hold the view that following a period of explanation, a series of questions should be asked in simple language or key points to check whether they have understood." (Newton and Appiah-Poku, 2007: 152)

Yet another states regarding the challenges faced when trying to make patients understand within developing countries:

"It is not only illiterate people who have problems understanding this, even educated people have the same problem and so you have to go to great lengths to explain what you are about, otherwise you might think that you have consent when in actual fact you do not have consent."(Newton and Appiah-Poku, 2007: 153)

By expressing their opinions the researchers are perhaps stressing that participants need to understand all information presented to them. This may not happen in some cases yet, the consent given in these cases may still be classified as being a valid consent; for example, when a potential participant deems some information irrelevant to his or her decision to enrol into a trial, then that information should not be forced on that particular participant. The participant may still make an informed, valid decision under these circumstances

because as mentioned earlier, people's decisions originate from a multitude of factors and are not based solely on information received from the researchers and their team. Therefore, asking all participants to fully understand all information presented to them in my opinion creates an impossible informed consent process.

One way of measuring how well potential participants understand the material presented is to hold interviews where researchers ask participants' questions that test their level of comprehension and make sure they have no misconceptions attached to their decision. If the potential participants show that they understand the basics of the trial then asking for their informed consent seems fair. If however, the potential participants show misconceptions, for example if they still see the trial as a means of treatment, then the research team should schedule extra meetings with those potential participants until these misconceptions are removed. When these potential participants demonstrate an improved level of understanding during a follow-up interview then they may be enrolled into the trial at that time. However, researchers reserve the right to politely dismiss those who continue to misunderstand the essence of the trial and prevent them from participating (Coletti et al., 2003).

Therefore, the comprehension of potential participants can improve by researchers and their team devoting more time and effort into making participants understand the whole purpose, process, benefits and risks of the research at hand (Flory and Emanuel, 2004; Gilman and Garcia, 2004). Furthermore, innovate methods could be used during the presentation of the trial information, for example flow diagrams to explain the risks and benefits (Wood, 2001).

Further points which researchers need to assure that participants understand include the duration of participation and availability of treatment in the post-trial period. These points need to be made clear to the trial participants prior to their enrolment into the trial. Although the importance of these points may not come to the surface except at the end of the trial, it is essential that potential participants are aware that their participation in the trial and therefore reception of certain medical interventions are linked to their enrolment into the trial only and will not be continued once the trial has ended. As stated earlier, certain populations link contact with health care providers as a chance of cure and do not understand the concept of research. In these circumstances it is important for researchers and their team to clarify the difference between the roles of the researchers and the physicians as well as the cessation of the provision of the treatment at the end of the trial. Presenting this information at the beginning of the interaction or during the discussion stage, stresses the importance of that information to the potential participants.

Furthermore, it is wrong to assume that information to potential participants may only be provided verbally. The same information may be provided in written form or any other form which the researcher/sponsor deems appropriate. This provision of information through different means provides more chance to the potential participants to understand the information being given to them and hence a better chance of achieving valid consent rather than simple consent.

After being provided with the required information, potential participants should then be given the time to digest and understand the material originally presented during the discussion sessions (Cox, 2002).

Community consent:

Under this heading it is sometimes argued that prior to the initiation of the trial, the community has to be involved and briefed about the trial and the consent of the community should be obtained regarding that trial. Rules of the FDA and NIH include the consultation of the community prior to the initiation of a given trial within a specific community (FDA, 1997, NIH, 1996). This is seen as a positive approach which is beneficial to researchers/sponsors, the potential participants, as well as the trial itself. The importance of this approach becomes much more important when the researchers/sponsors are not members of the community or are not familiar with the customs or preferences of that specific community. The NBAC states:

“Researchers should consult with community representatives to develop innovative and effective means to communicate all necessary information in a manner that is understandable to potential participants.”(NBAC, 2001: 3.5)

Although this is an important step to undertake, it is not the focus of our discussion in this chapter. Hence community involvement in the assessment of the appropriateness or acceptability of a given trial to a certain community will be discussed in further detail in chapter five when discussing the role of the RECs and the involvement of the community where the trial is to be carried out. Further discussions here will focus on the replacement of individual consent by that of the community representative or leader.

It is well accepted that adults in industrialised countries with decisional making capacities must give their own consent to participate in any kind of treatment including interventions associated with research (Emanuel et al., 2000). Informed consent is grounded into respect for person as per the definition of the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research which defines it as:

“Respect for person incorporates at least two basic ethical convictions:
First of all, the individuals should be treated as autonomous agents,
and second that persons with diminished autonomy and thus in need
protection are entitled to such protection” (Belmont report, 1979).

Autonomous individuals are those capable of making decision on their own without interference or hindrance from others. They act as moral, rational agents (Levine, 1991). This approach is reflected in several documents including the NBAC:

“Where culture or custom requires that permission of a community representative be granted before researchers may approach potential research participants, researchers should be sensitive to such local requirements. However, in no case may permission from a community representative or council replace the requirement of a competent individual’s voluntary informed consent” (NBAC, 2001: 3.7)

The approach taken by these documents is that community consent should be viewed as an important step in the recruitment process since it has its own advantages however, community consent should never replace the informed decision of an individual participant.

Individual autonomy should be considered as a value on its own, and emphasise the role of researchers and their team in ensuring that participants make decisions suitable for them through the process of counselling. Therefore, the view is that the research team should regard community consent as an initial step in the informed consent process and not as a true consent on its own. However this approach does not necessarily show respect for person within all cultures and it may not even accomplish its purpose within all cultures within developing countries.

Since we have mentioned earlier that developing countries form a heterogeneous group of communities and populations, it is understandable that their views regarding personal autonomy and respect for an individual's decision will be different as well. Some communities respect this autonomy and a person has the right to make his or her own choices. Within these communities, the researchers will have no problem in obtaining individual consent. In other communities however this is not the case.

In some societies within developing countries, the community holds a key value. The individual person's being is defined by his or her belonging to the community. The individual person exists in terms of their family, clan, and whole ethnic group. This has been observed by some writers, for example Mbiti, quoted by Veatch, who states:

“Only in terms of other people does the individual become conscious of his own being, his own duties, his own privileges and responsibilities towards himself and towards other people. When he suffers, he does not suffer alone but with his corporate group: when he rejoices, he rejoices not alone but with his kinsmen, his neighbours and his

relatives whether dead or living Whatever happens to the individual happens to the whole group, and whatever happens to the group happens to the individual. The individual can only say 'I am, because we are, and since we are, therefore, I am' " (Veatch, 2000; 349)

Within these communities the individual's identity is born through the group he or she exists within. Hence an individual's life is not considered a personal property but is rather owned by the group. The person is seen as a "link in the chain uniting the present and future generations" (Veatch, 2000: 349). Therefore health is the concern of the whole community and its preservation by the individual is expected for the good of the group. Individual consent has no meaning. Tribal or community consent; or the consent of a single person on behalf of many others is taken as the norm in these settings where community as a whole is valued more than individuality (Moody, 2002). In yet other places, the husband consents on behalf of his wife because her consent is simply not recognised. Therefore, beneficence, as a principle has more value than individual autonomy. When it comes to health care, although health is highly valued, the good of the group or community is weighed against the needs and interests of the individual. The provision of health is not directed at the elimination of disease from a single person perspective but rather focuses on the individual's whole including his or her role and involvement within the community. It is perhaps understandable then to note that within these societies individual autonomy and ability to act independently is limited by the importance of communalism. There is interdependence between the members of these communities and an individual has certain obligations towards that community. An individual who disregards the role of the community is regarded as anti-

social. This does not mean that an individual does not have an independent personality and a certain degree of autonomy within such communities does exist. However this autonomy should not fall outside the traditional norms of the community. A person is expected to conform to communal decisions. At the same time, the community restricts the actions of a certain individual if his or her actions are considered to be against his or her own good. In other words the community may exercise paternalism when the good of the individual contradicts the more important good of the community.

These cultural differences may make it very difficult to take individual consent. In an attempt to balance between demanding individual consent and completely dismissing it, the CIOMS proposed:

“Where individual members of a community do not have the necessary awareness of the implications of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader”
(CIOMS, 2002: article 15)

Sometimes, a research team intending to carry out their research in a particular community within a developing country makes first contact with the community leader. Obtaining the consent of the community leader may be seen as a positive approach because it may serve as an outreach to the community. The community may gain improved understanding of the research when the researchers/sponsors as well as the research team hold several meetings

with the community leaders to explain the details of the research. This in turn shows the community that the researchers and their team respect the community, which may reflect positively on the cooperation given by the community towards the researchers in the end. As Diallo states:

"There are thus intrinsic ethical reasons, such as the need to respect communities, for adding community permission to individual informed consent guidelines as a requirement for ethical research involving communities. There could also be instrumental ethical reasons to add this requirement; community permission could enhance the individual informed consent process, perhaps improve enrolment, and decrease adverse effects of the research on community values." (Diallo et al., 2005: 256)

Presenting the trial through this process may actually help in the recruitment of participants for the research. Once the leader of the community understands and supports the research, selling the idea to other members of the community becomes an easier task and potential participants may become more encouraged to enrol into the trial. This step in and of itself is not problematic since it aims at providing more information to the community through the person representing it. Problems do arise however when community consent is seen as having sufficient importance to replace the necessity to obtain individual consent.

After obtaining community leader agreement for the involvement of individuals within the trial, researchers may still need to provide certain information about the nature of the trial

and its procedures to the community members or the potential participants. However, certain individuals may not want to receive such information. They may believe that since the leader gave his consent, then there is no need for them to give their agreement as well. These individuals should not be forced to receive undesired information especially if it is perceived as defying the leader's instructions. Objections to this approach to informed consent focus mainly on the first meaning of informed consent presented earlier by Beauchamp and Childress and the autonomous authorization of the individual. However what we should be focusing on is the second meaning of informed consent which is the social rule of consent. Individual consent is not authorized by the community and may not even be appreciated by the individual potential participants themselves. The social rule of the provision of a community leader of consent on behalf of the members of that community may be acceptable. Empirical data shows that individuals within developing countries are not as interested in making decisions for themselves as theorists assume (Degner, 1992; Ende, 1989). This is not to say that the authorization of the individual potential participant should not be obtained since there may be individuals within the community who may not want to be recruited into the trial.

A process which could make sure that the participants still receive enough information about the trial could be the holding of an open meeting with the community in the presence of the community leader where information is presented to the community members about the trial in the presence of the research team. This event could also be taken as an opportunity to answer questions which may arise and to clarify certain points regarding the trial. Some writers argue that even when tribal consent is obtained, individual consent can be acquired

later on in the process (Barry, 1988). Although individual autonomy is considered essential especially in clinical trials in industrialised countries, it is not necessarily seen that way within certain communities. Members of a certain community who are not accustomed to giving their own consent may view the insistence on individual consent as an insult to their leader. In such cases, cultural respect should be expressed by accepting the differences in the perception of the importance of individual consent within different communities. The insistence on individual consent may lead to the failure in the recruitment of potential participants into potentially beneficial trials especially in socially valuable ones. The anticipated health benefits are of more value than the individuals exercising their personal freedom and providing their consent. Within these special circumstances, the researcher could submit a proposal to the REC outlining the intention to obtain only community leader consent and the justifications for waving individual consent. At the same time the local REC, if it is in charge of reviewing the trial proposal, as will be argued for later in chapter five should be understanding of the circumstances and allow for such alterations.

Having said that, certain objections may be anticipated regarding the acceptance of community consent on behalf of individual members of that community and hence the research team needs to ensure that community consent is truly representative of the choices of the community members. The easier scenario to be presented is where the community has a benevolent leader, then the decision made to enrol the community members into a given trial may in fact be in the best interest of the community members. Alternatively, a more problematic scenario, from the perspective of the researchers may exist where a dictator community leader exists who may not consider the best interest of the community

member and may force the community members into trials that they do not desire to be enrolled into. In such instances, the research team has to ensure that the community members authorize their participation in the trial and are not merely forced by the community leader. One method of ensuring potential participants' authorization could be the settings of private discussions between the potential participants and the research team member on individual basis. These discussions could be done at the time of initial assessment of the potential participants in order to avoid suspicions being raised by the community leader or other community members which may reflect negatively on the concerned potential participants. These discussions have to be done by the original research team rather than be designated to a trained local research team member. This step is essential because in cases where discussions are held with local team members, the fears that the potential participants may have from rejection of participation may still exist and their agreement to participate may not be a true choice. The fear that potential participants may have from the dictator leader may still exist when dealing with a local research team member. The same fear of transmission of the information shared between the potential participant and local research team member to the community leader and the fear of consequences of refusal to participate in the trial may prevent the participants from sharing their true decisions with the local research team members. Of course this fear may still exist when discussions are held with the original team members, however the research team must strive to eliminate, or at least reduce, sources of force or pressure that may affect the potential participants' choices. Through these private discussions, the research team may be approached by certain members of the community who do not want to participate in the

research but lack an ability to voice their concerns in public. These cases may exist regardless of the type of community leader the research team is dealing with. In such cases the research teams hold the responsibility of making sure that these individuals' speak freely and express their opinions without fear of being overheard and perhaps punished for their opinions, or for disobeying community leader orders. The research team should exclude these individuals from the research and should not force them to enrol into the trial. The justifications presented to the community leader for this exclusion could be based on scientific reasons rather than the declaration of the individual's refusal to participate.

The biggest challenge to the research team however is the assessment of the kind of community leader they are dealing with and his relationship with the community members in order to assess whether the decision made are in the best interest of the community members or not. However, the best interest of the potential participants and social value should have been assessed during the review process by the local REC.

Getting a trial underway could escalate into something more problematic in cases where leaders withdraw community consent after it has been provided or refuse to grant permission for a trial in the first place. Both situations present challenges to the researchers/sponsors and may have disappointing outcomes for the researchers/sponsors. In cases where a community leader provides initial consent but then later decides to withdraw that consent or permission, then that decision should be made known to the participants (Diallo et al., 2005). Many of the participants may decide to withdraw from the trial based on the community leader's withdrawal. However; there may still be members within the community who would want either to be enrolled into the trial even if the community leader

refuses the trial proposal or those who want to continue their participation in the trial after the withdrawal of the community leader's consent. If these members are willing to participate in the trial, despite the social consequences of their participation and regardless of the difficulties they may have with their community, then these members should not be denied access to or be excluded from the trial on the basis of the community leader's decision

If on the other hand, the community leader refuses to grant permission or consent in the first place, then researchers will face a much bigger challenge. Admittedly, the researchers can anticipate a much bigger challenge in recruiting the required number of participants into the trial and may decide to do their research in another place where it will be perhaps easier to convince locals of the trial merits. Although individual autonomy holds high importance the researcher's autonomy should also be valued. If a researcher feels he or she will experience an easier time recruiting participants and conducting the trial in another community then the trial should move to that community provided that the participants are recruited based on scientific need rather than convenience alone.

Hence, community consent should be viewed as an important step in the recruitment process because dealing directly with the leaders may help researchers better understand the trial's value to the society, improve participant understanding about the trial and may even increase enrolment.

Conclusion:

This chapter discussed procedural fairness from the perspective of assurance of procedural aspects of informed consent. The highlights of the chapter included several points. The first one was the emphasis on the importance of communication between the researchers and their teams and the potential participants rather than the amount and content of information being presented. Another point of emphasis within the chapter included the assurance of the researchers and their teams that the potential participants are in a deliberative mindset during the negotiations or information presentation process, the provision of information in different forms and the adaptation of new methods of documentation of individual consent. The importance of community consent within certain communities within developing countries has also been presented with attention being made to certain exceptional individual cases where the potential participants may not agree with the community leader's decision.

Informed consent is an integral part of fairness to the potential participants. The assurance of fairness through informed consent comes in the form of assuring procedural fairness while obtaining informed consent from the potential participants. Although the informed consent process is a thorny one especially in developing country settings, accomplishing an acceptable level of potential participant understanding could still be achieved, but perhaps with some extra effort on the part of the researchers and their teams. Although poverty, vulnerability, poor access to health care services, and low levels of educations may act as large obstacles in the process of obtaining informed consent, an acceptable level of understanding can be achieved despite these obstacles.

Informed consent should be viewed as a process rather than something the researchers and their team expect to accomplish in one step. However the many other issues faced by researchers in developing country settings further complicate the process. The procedure in its entirety involves inviting the potential participants to the trial, providing them with the needed information, explaining the information to them over several sessions using different methods, giving potential participants time to consider all the information they have received, and finally respecting the individual's decision whether to participate or to decline participation.

More importantly, and before the provision of information to the potential participants, the researchers need to assess the mindset of the potential participants and ensure that they are in a deliberative mindset. This ensures that the potential participants do not underestimate the level of risk or overestimate the level of benefit expected from the trial. Still some misconceptions held by the potential participants need to be directly addressed such as the therapeutic misconception. Other misconceptions may be indirectly addressed by the awareness of the researchers themselves about the kind of information they emphasize during the disclosure and communication process.

Furthermore, the method of documentation of the potential participant's agreement may be given in forms other than writing. In some cases verbal, witnessed, and videotaped consent by reliable sources could replace the written form. This approach may hold special importance to potential participants in developing countries living under oppressive regimes who see signing in general as a threat to their safety and property. Overall, the validity of the

consent should be the focus of the researchers and their team rather than the signature of the consent forms.

Finally, within some developing countries, community consent bears more weight than individual consent. In these situations, the researchers and the sponsors should respect the cultural differences that exist within these societies and not to try and force the western standards of individual consent as a necessity.

Chapter Three: Outcome Unfairness

Introduction

This chapter will focus on the second kind of unfairness: namely outcome unfairness. The discussions within this chapter will focus on the anticipated end results on the parties involved within the interaction. These effects may include benefit, harm, or no effect on either or both parties involved. The chapter will conclude that the acceptability of the potential harms associated with any given trial proposal are best assessed by the potential trial participants and/or the communities involved. In addition, the tools for the assessment of these harms will be provided. On the other hand the benefits of a given trial need to be assessed from different perspectives. It will be shown through this chapter that in order to label a trial as a being beneficial, the social value of that trial needs to be assessed in the first place. The chapter concludes that despite the possibility that interactions between researchers/sponsors and potential trials participants may be beneficial, there may still be a need to prevent these interactions from taking place based on the strategic intervention argument which states that even mutually beneficial interaction may be prohibited on the basis that non-exploitative interaction be promoted.

Outcome unfairness looks at the effects of the interaction on both parties involved. This is what Hawkins and Emanuel refer to as degrading wrongful interactions. Within clinical trials the interaction between researchers and potential participants may harm, benefit, or have no effect on either party. In order to assess the risks and benefits of that interaction we need

to either assess them from an ex-ante perspective or an ex-post perspective. The ex-ante perspective requires us to assess harm and benefit from the perspective of the researcher or the potential participants before the interaction is initiated. This means we need to assess anticipated outcomes of harms and benefits. On the other hand, the ex-post perspective requires us to assess harm and benefit based on actual results of harm or benefit at the end of the interaction. However before we decide which perspective we are going to adopt in order to assess the outcome of the interaction between the researchers and the potential participants, we need to be clear about the goals and aims of clinical trials in the first place.

Research is defined as a “systematic investigation designed to develop or contribute to generalizable knowledge. (LO, 2010: 7). Hence by definition, research is primarily intended to benefit future patients by generating new scientific knowledge and not the participants of the trial directly despite the fact that some of the trial participants may benefit directly from their enrolment into the trial. What is expected from the researcher/sponsor is that the trial be done in a scientifically valid method in order for the findings to be valid and for the knowledge to be disseminated to others such as physicians, scientists, and future patients in order for them to benefit from that knowledge.

The participants recruited into the study experience risk ranging from minimal (for example inconveniences and intrusion of privacy and confidentiality) to more serious medical complications. The question posed by the research cannot be answered except after the study is complete and the harms or benefits are at best anticipated and not known with certainty. This is why harms are referred to as potential harms and benefits as expected benefits. They are not guaranteed. Hence the best assessment of the outcome of either

benefits or harms would be from an ex-ante perspective. Since we are considering clinical trials and whether they should be approved or not, I will focus my discussion of outcome unfairness from an ex-ante approach.

By focusing on the outcome of the interaction we need to assess the effect of the interaction on each of the parties involved within the interaction. In referring back to the definition of exploitation, taking unfair advantage of someone means that there has to be some form of benefit to the exploiter. Indeed some definitions of exploitation imply a net gain by the exploiter as a necessary requirement for exploitation such as. Wertheimer's quote of Tormey mentioned in chapter one. Although I agree that the researcher/sponsor must gain from the interaction with the participants, not all interactions which benefit the researchers/sponsors are balanced by a loss on the part of the participants. The benefits the researchers/sponsors gain from the interaction may take a variety of forms. Although financial gain is the most obvious and discussed as a form of benefit to the researchers/sponsors, it is certainly not the only kind of benefit. Generating new information, publishing trial results, acquiring patency rights, and obtaining academic recognition are some of the researcher/sponsor benefits that may result from their interaction with the participants. This benefit may be unfair if it is obtained through the unfair taking advantage of the participants or when the researcher/sponsor gains an unfair or excessive share of the benefit when compared with the benefit to the participants or when there is an unfair division of the benefits between the parties involved. It has to be emphasized though that we are not talking about even division of the benefits between the parties involved; rather it is the fair division of the benefits that is important. This point will be further discussed in more detail in chapter four which focuses

on post-trial benefits. However, even if we assume that the researcher/sponsor always stands to gain from the interaction with the trial participants, the interaction itself cannot be labelled as being unfair simply due to this benefit. Hence a detailed look at the effects of the interaction on the trial participants also needs to be done.

Effects on participants:

It is anticipated that the interaction between the participants and the researcher/sponsor has one of three possible outcomes on the participant, each of which will be discussed individually:

No effect:

During a “no effect” type of interaction, otherwise referred to as "harmless parasitism", the researcher/sponsor benefits from the interaction while the participant experiences no affect whatsoever (Feinberg, 1990). They neither benefit nor are they harmed by the interaction. To illustrate the point consider a person (A) following the taillight of another person (B) while driving during a foggy night. Here (A) benefits from his interaction with (B), (B) does not consent to (A's) actions, and we assume that he is not bothered by (A's) headlights. In clinical trials however, such cases rarely take place because the interaction commonly entails some kind of harm or benefit to the participants. Hence this anticipated outcome of the interaction will not be further discussed.

Harmful effects:

Harm or risk in its broadest definition means the harm or injury occurring as a result of participation in a trial. The term “risk” may be used in two different ways (Iltis, 2005). From an absolute perspective, the term “risk” is used as a number representing the probability of some event occurring. In another sense “risk” may be used to define the character of a risk and address questions like: What harms are possible? Are the risks temporary or permanent? How much damage would they cause? Etc. It is the second meaning of the term “risk” which concerns us here.

Risk takes on many different forms, and should not remain narrowly associated with physical harm only. Other forms of harm to potential participants may include psychological, social, as well as economical harms. The level of risk can also range from minimal to severe. Some definitions of exploitation take the infliction of serious harm on the participants as a necessary condition for exploitation to exist within an interaction (Munzer 1990). There are several reasons why this definition is incorrect. The first reason is that the definition links between exploitation and serious harm so exploitative only exists if the participants are at risk of serious harm. This is not true since some exploitative interaction may only expose participants to minimal harm but may still be labelled as exploitative. Also, not all risk is ethically problematic. Some forms of serious risk may have ethical acceptance whereas some lower risk studies may not be ethical.

The second reason for rejecting the serious harm argument is that harm itself is not always present within exploitative interactions. In some exploitative interaction, the participants

may anticipate benefiting from their recruitment into the trial. In this case, despite the fact that the potential participants will not be harmed, the interaction may still be considered as exploitative.

When harm does exist within an interaction, the harm has to be a direct result of the participation within the interaction. In the “harmful effect” type of interaction, the participants become harmed through their interaction with the researcher where the interaction makes them worse off. To understand what worse off really means, we need to adopt the ex-ante perspective mentioned earlier. Therefore, when we say that the participants are “worse off” we mean that their status at the end of the interaction is expected to be worse than their initial status prior to the interaction with the researcher/sponsor. If the participants’ situation or condition deteriorates as a direct result of their participation in the trial, then they are harmed by that interaction. On the other hand, in some situations, if the participant’s condition remains the same, before, during, and after the trial, then apparently the participant does not sustain harm. For example, participants of the AZT trial who were allocated within the placebo arm of the trial were at risk of harm of transmission of the HIV infection to their foetuses however this harm does not exceed the harm that exists outside the scope of the trial. Similarly, the Surfaxin trial participants allocated within the placebo arm of the trial may be harmed through their exposure to the illness itself, however that harm does not exceed the harms the same participants are exposed to outside the scope of the trial. However the participants involved in the placebo arms of both trials stand to benefit from the medical services and examinations offered to them throughout the course of the trial.

It is also important to point out that the harms suffered by the participants may come about as a result of the deliberate actions of the researchers and not through the participation within the trial or the medical condition being investigated. In some cases, the researchers may deliberately hinder the improvement of the condition of the participants. This deliberate prevention of improvement could be considered as a form of harm. The best example of such a situation is the Tuskegee Syphilis study where the researchers not only deceived the participants by making them believe they were being treated for a certain medical condition, they also prevented them from receiving effective treatment for their condition when it became available (Jonsen, 1998). The harms inflicted on the trial participants not only included their deception and failure to provide effective treatment when it became available but also included harming them through their prevention from obtaining effective treatment outside the scope of the trial.

Furthermore, it is important to distinguish between the harms directly caused by the enrolment within a trial and the deterioration of the condition of people excluded from the trial. While the first category is said to be harmed by the trial, the same cannot be said about the second group. Although there may be some deterioration within the condition of the excluded populations, this is caused by the conditions that exist outside the boundaries of the trial and not by the trial itself. These specific conditions exist regardless of enrolment into the trial and hence, the excluded individual is not made worse off as a result of the exclusion. Hence the harm to the potential participants is not a factor which could lead us to label an interaction as being exploitative. There are other factors which play a role in this analysis which will be discussed later on in this chapter.

Beneficial effect:

Although it may be difficult to comprehend, some exploitative situations may benefit the participants in a similar way to the benefit of the researchers/sponsors.

"Exploitation can be entered into voluntarily, and can even in some sense, be advantageous to the exploited party." (Levine, 1988: 66)

The benefits to trial participants may take different forms even when assessed from an ex-ante perspective. It is necessary to assess the expected benefits to participants with relevance to the participant's situation prior to the interaction. Within clinical trials participants in developing countries benefit from trial enrolment because they receive treatment for an illness they suffer from, or they gain access to health care services that may improve their health status.

So, from an ex-ante position, those involved in the interaction experience an improved status when compared to their situation outside the scope of the interaction. In some cases, the participants' anticipated benefits far exceed those expected for the researchers. A person who receives treatment for a life-threatening condition will regain his or her health, a priceless gift for most people if not all. The researcher stands to gain materially and morally, but humans attach far more value to good health.

Types of exploitative interaction:

Applying what has been said so far about the effects of the interaction on the parties involved and anticipating either the existence of the participant's consent or its absence four different possible combinations of these factors are generated (Wertheimer, 2010: 201):

1. Harmful non-consensual interactions
2. Harmful consensual interactions
3. Mutually beneficial non-consensual interactions
4. Mutually beneficial consensual interactions

To further understand the difference between them, a detailed discussion of the different possibilities will be given below. Due to the similarity between the harmful interactions, whether consensual or non-consensual, the discussion will combine the two kinds of harmful interactions in one section. The same will be done for mutually-beneficial interactions.

Harmful (non) consensual interactions:

We have defined harm as the risk the participants are exposed to as a result of their participation in the trial and it can range from minimal to severe harm. Risk can be defined as minimal when the probability as well as magnitude of the risk remains at an equivalent level or is lower than those risks encountered in daily life, or while performing ordinary physical or psychological examinations or tests (Wendler and Miller, 2007). It is generally accepted that a vulnerable individual incapable of consenting to trial participation should not be exposed to risks that exceed a minor increase over minimal risk. However there is a lack of international

regulatory agreement concerning the acceptable level of risk to which adult participants with decisional capacity may be exposed to.

The proposal put forward by Wendler and Miller offers a comprehensive and clear stepwise approach for assessing ethical acceptability of various risks within trials (Wendler and Miller, 2007). This method offers more insight into acceptable trial conduct than the traditional approach of classifying research into either therapeutic or non-therapeutic. In the latter case, therapeutic trials get approved when they satisfy clinical equipoise whereas “non-therapeutic” trials may receive approval even when they do not serve the best interests of the participants. This traditional type of approach suffers from a too rigid differentiation of trials based on two types of research which in reality may be hard to distinguish. The fact that any therapeutic research has non-therapeutic components adds an additional level of complexity. Wendler and Miller call this proposed method the “net-risk test”, which includes three steps:

1. Identifying the net-risk interventions:

The initial step entails identifying the individual interventions within the proposed trial. The risk-benefit profile of each intervention is assessed by comparing its risks with potential clinical benefits for participants. Also the risk-benefit profile of the proposed interventions is compared with the available alternatives outside the scope of the trial. In some cases alternative interventions may not exist. If the assessment shows that the risk-benefit profile is at least as favourable as that of another available intervention, then there is no net-risk. However, if the risk-benefit profile comes out less favourable than existing interventions then conclusions point to a net-risk. According to Wendler and Miller “the magnitude of the

net-risk is a function of the extent to which the intervention presents increased risk, or decreased potential benefits compared with available alternatives.” (Wendler and Miller, 2007: 484). For example the AZT trial, involves comparing the active agent (AZT) with placebo. If we focus on the active arm of the trial, then the risks of this specific intervention may include lack of effectiveness. On the other hand the risks associated with placebo use in the trial include risk of transmitting HIV infection from mother to foetus, as well as death from the illness and superimposed infections.

According to Wendler and Miller we must compare the risks of these two interventions with the alternative available interventions (Wendler and Miller, 2007: 484), a situation which creates two possible scenarios depending on how we apply the term available intervention. Within the first possible scenario we compare the trial with the available intervention within the developing countries for the prevention of HIV transmission. In these settings no intervention exists for the treatment of this condition and therefore the risks to the participants in the placebo arm of the trial are equal to the risk which the rest of the population, outside the scope of the trial, are exposed to. The benefits however, include the reduction in the maternal-foetal transmission of HIV meaning a reduction in the number of deaths. Therefore the net-risk presented by the AZT trial, in this scenario, is at least as favourable as that of the available intervention and the trial will have no net-risk.

The second possible scenario would require us to compare the AZT with the available intervention in more developed countries, namely the ACTG 076 protocol. The effectiveness of the ACTG 076 has been proven through previous trials and its use has been implemented within more developed countries. The participants enrolled into the active arm of the trial

where ACTG 076 would be provided to them, will be at a much lower risk of being exposed to harm or the transmission of HIV infection from mother to foetus. On the other hand, the risk to the participants receiving the target agent (AZT) will be at a higher risk of transmission of the illness given that the effectiveness of this agent has not been proven yet. Still this does not mean that the participants who receive AZT are exposed to a net-risk given the alternatives available outside the dimension of the trial. As mentioned earlier, no treatment modality exists within some developing countries to prevent the transmission of HIV from mother to foetus. Hence even when enrolled participants receive the AZT, they are better off than the population outside the scope of the trial if AZT proves to be effective. On the other hand, if the AZT does not prove to be effective, then the enrolled participants have the same risk of maternal to foetal transmission of HIV as the general population within the same settings. This leads us to conclude through using Wendler and Miller's identification of the net-risk that whether we use placebo or ACTG 076 that there is no net-risk within the trial.

Similarly, the assessment of the Surfaxin trial's net-risk assessment requires first identifying all the interventions that are included in the trial. Investigators choose two interventions for use in the Bolivian trial arm, Surfaxin and placebo. The effectiveness of Surfaxin equals other existing effective interventions available for the treatment of RDS, and it is considered a low risk treatment. The placebo arm of the trial however poses significant risk to the trial participants, including the risk of death. However when we compare the two arms of the trial with existing interventions within Bolivia, we find out that no interventions were available for the treatment of RDS at Bolivia at the time the trial was intended to be carried out. So the risks to the trial participants, even those in the placebo arm were not increased compared to

risks afforded by available intervention within that setting. Hence there is no net-risk in the Surfaxin trial as well.

2. Assess the net-risk interventions:

The next step in risk assessment considers whether social values gained from the trial outweigh risks posed by the net-risk assessment. Hence, a study with a low net-risk, but also without social value may not be approved, whereas a study with a net-risk that also offers social value could receive approval. If we apply this to the AZT trial we can see that the trial would add a very important social value. This social value is represented in the reduction in maternal to foetal transmission of HIV infections whether we are considering a placebo or an active controlled trial. However, since the placebo arm of the trial bears no net-risk then the placebo controlled trial will add greater social value given that the ACTG 076 has been rated too expensive to be made available for the population by their governments even prior to the initiation of the trial. There is no point in proving its effectiveness or superiority to AZT. We know even before designing the trial that ACTG 076 is more effective than AZT. What would re-proving this point provide to the target population? The aim of the AZT trials is to find a shorter, effective, and more affordable course of an anti-retroviral agent which would prevent or reduce the transmission of HIV infection from mother to foetus. The relevant research is very much needed because limiting maternal to foetal transmission of HIV is vital for preventing needless suffering and death. The information gained would help immensely towards improving health care in the population intended to benefit from the trial in the first place. Hence considering the social value, the AZT trials, and the discussions in the previous

section, we reach the conclusion that the placebo controlled AZT trial is the better option especially since no net-risk exists and the anticipated benefits are high.

The Surfaxin trial on the other hand is different. There are many available pharmaceutical agents for the treatment of RDS all of which are effective, but expensive. Although it could be argued that since there are no alternative modalities of treatment within Bolivia for RDS, then the use of placebo is justified. However, because the results of the trial were never intended to benefit the research population i.e. the infants in Bolivia, this argument loses its strength due to the lack of social value. The results of the research were intended to benefit infants in developed countries only. The trial does not satisfy the social value criteria. Therefore, the risks of the trial are not balanced by the social value of the trial.

3. Assess the net cumulative risks:

Finally, the total or cumulative risk of the research as a whole warrants consideration. Although some interventions may present low net-risks individually, their cumulative risk may not meet acceptable standards. Therefore, the trial's cumulative risk should be taken into consideration. The Institute of Medicine also stresses the importance of this step by stating:

"Research may involve several different procedures that may involve minimal risk or burden individually, but that may present more than minimal risk when considered collectively." (IOM, 2004)

Within the AZT trial, while looking at the overall risk imposed by all interventions within the trial we can see that a cumulative risk exists for the transmission of HIV infection from

mother to foetus, which may be labelled as excessive. The same could be said for the participants enrolled in the placebo arm of the Surfaxin trial. However, once again, the risk to the participants in both trials does not surpass the risks they are exposed to outside the trial considering the available interventions within the local setting.

Although Wendler and Miller offer a clear stepwise analysis of risk, the approach fails to define what "excessive risk" means. Many problems crop up during a risk assessment. For example, sometimes insufficient knowledge about the potential risks associated with a trial makes clear judgement difficult. At best, these risks can be labelled as "anticipated". Furthermore, other unforeseen risks may occur while the trial is taking place and these surprises may cause shifts in the risk: benefit ration, and possibly result in the termination of the trial if they are serious enough. It is also difficult to standardize risk assessment because individuals evaluate risk in different ways based on their own knowledge and experiences. Many factors may cause assessment variations including misconceptions, lack of information, or most commonly differences of opinions about the foreseen discomforts associated with an intervention.

There is no consensus as to what constitutes acceptable risk to adults with decisional making capacity. Societies usually allow such adults to participate in high risk activities if their actions benefit society in general for example fire fighters. Individuals who agree to take on such high risk professions do so knowingly and accept the risks. In addition, the benefits gained from these professions, ranging from pay to moral reward, lead to a reduction in the net-risk. This combination justifies the acceptance of the concerned individuals to the risks involved with their choices. By analogy, we can allow other individuals with the same decisional

capacity to undertake excessive risks as long as social values (net gain) justify the risks or reduces the net-risk. Some potential participants may consent to participate in trials with high risk whereas others may refuse to participate in trials with minimal risk. This individual preference gains official status in the form of valid informed consent. We have to emphasize however that once potential participants are given the responsibility of assessing risk, researchers have to ensure that they are in a deliberative mindset to avoid distorted perception and assessment of risks and benefits.

Non-consensual interactions are disrespectful and since respect is shown through the allowance or non-interference with the person's autonomy or decision making, then these interactions can be defined as unfair from a procedural perspective since they fail to initiate the process of obtaining valid informed consent from the individuals in the first place. However, there are certain exceptions such as observational studies where the knowledge of the individual participants about the trial may lead them to alter their behaviour. In such cases, the consent of the individual may not be obtained prior to the initiation of the trial; however the participants deserve to know that they had been part of a trial and the purpose of it at the end of the trial. Other instances where obtaining consent from the potential participants may be waived are trials aiming to recruit non-autonomous individuals. Also, in trials focusing on emergency situations where the consent of the individual cannot be obtained at the time may fail in the requirement for informed consent. This does not mean that these trials are disrespectful for the participants rather they are seen as exceptions to the rule. However even then the exception has to be justified and approved by the REC.

Within normal types of trials obtaining the consent of a person shows respect to that person by allowing them to choose what they believe to be the right decision. Considering all that has been mentioned earlier, it becomes clear that informed, valid consent should take precedence in such cases and the individuals themselves should assess whether they want to take on the risks or not.

Mutually advantageous (non) consensual interactions:

Once again the focus here is on two aspects of the interaction, the consent of the individual and the outcome of the interaction. Non-consensual interactions, except within restricted situations amount to unfair treatment and therefore exploitation. On the other hand, the outcome of the interaction here is beneficial to the participants and therefore, does not fit the criteria for unfairness from an outcome perspective. Within such interactions participants themselves actually benefit from their participation. This benefit is translated into the improvement in their health status. They also give their consent for the enrolment within the interaction. Yet these beneficial interactions are not cleared from accusations of being exploitative despite the potential benefit to the trial participants.

Although the lack of benefit within the interaction may make us more suspicious about the interaction, the existence of benefit does not mean that the interaction is non-exploitative. Therefore, even with the potential of benefit to the trial participants, the interaction itself cannot be said to be non-exploitative. There is still a missing link. It could be anticipated that an argument which defends the allowance of consensual mutually advantageous interaction could be brought forward. This argument could state that since participants have consented

to mutually advantageous interactions then we have no business prohibiting them regardless of whether the trial is to be carried in a developing or a developed country. What this line of argumentation fails to recognize however is that although consent is important, it does not exclude exploitation from an outcome perspective. Otherwise we would not have classified unfairness from a procedural and outcome perspectives. Informed consent is important and hence the distinction between consensual and non-consensual interactions between participants and researchers/sponsors. A situation where both parties agree to be involved within the interaction and provide informed consent represents one form of consensual interactions. In cases where participants give their informed consent to be enrolled into a trial, exploitation may still exist, unless we are arguing that a person can never consent to take part in exploitative interactions. This is apparently not the case since many exploited individuals or groups may consent to the exploitative interaction.

Arguments more relevant to developing countries and exploitation revolve around the concept of the harsh circumstances that surround those participants. These arguments state: potential participants are already surrounded by harsh circumstances and their participation in a mutually advantageous interaction may be the only gateway to benefit, so why would we want to deny these individuals of such a chance. Still arguments against the prohibition of mutually advantageous interactions stem from the perspective that these interactions, always benefit the participant, perhaps more than the researcher/sponsor in some cases, therefore the prohibition of these interactions would deny the participants such an opportunity. The counter argument to both of the previously mentioned arguments supporting mutually advantageous interactions can be realized if we focus our attention on

the circumstances that led to the interaction between the potential participants and the researchers/sponsors in the first place. By arguing that we should allow mutually advantageous interactions between researchers and potential participants, we are ignoring the fact that it is exactly those harsh circumstances existing within developing countries that escort the researchers/sponsors to do their research on those vulnerable populations. If those harsh circumstances did not exist in the first place, the researchers/sponsors would have done their research somewhere else. Given the fact that it is the vulnerabilities of the participants from developing countries that lead to their recruitment into the trial in the first place, we need to consider this part of the situation. Therefore even if we ensure that the participants gain from their interaction with the researchers/sponsors, we still need to consider the exploitation part of the interaction and whether we need to prohibit such interactions even if both parties consent to the interaction and benefit from it.

However, even with the potential benefit to the participants the interaction itself may still be unfair from different perspectives. Several arguments are presented to suggest the prohibition of even mutually advantageous exploitative interactions. These include: dignity and degradation, Kant's Universal law formulations, paternalism, prophylactic argument, and the strategic intervention. Each of these will be discussed individually in the following section.

Dignity and degradation:

Dignity connects with the idea that humans have certain fundamental needs, desires and attributes. Thus, to treat someone with dignity means recognising and respecting their needs, desires, and attributes. When talking about human dignity, we cannot avoid turning

to Kant's doctrine of "Respect for persons". Kant claimed inconsistency between treating an individual as a free and rational being and using them only as a means of satisfying one's goals, for to do so denies their dignity and autonomy. This analysis links to Kant's instrumental use. He believed that people should never simply be used only as a means to an end, but rather deserve at the same time to be treated as ends in themselves. He states:

"Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end" (Kant, 1785: 30)

The meaning of the injunction to treat and regard people not merely as means but also as ends, suggests that we ought to value people rather than see them as useful instruments for achieving personal goals. To decide whether the researchers/sponsors use potential participants instrumentally; we need to prove that they indeed use them as mere instruments. This use "as a means" relates to the concept of co-modification where one party uses the other as an instrument according to the acceptable processes of the marketplace. If we look at it this way, then according to the marketplace norm, both parties involved within the interaction use each other for their own benefit. The researchers/sponsors use the participants to answer their research question and generate knowledge. On the other hand the participants use the researchers to gain some benefits as well whether in the form of health related benefits that they may not be able to have access to through regular health care services or moral benefits through their knowledge of benefiting future populations if their participation is based on altruistic reasons. Due to the nature of mutual use, both

parties should bargain for the best outcome for themselves within that interaction. Researchers/sponsors bargain to gain the maximum benefit through the shortest period of time. On the other hand, research participants bargain to maximize their own benefit which may be directed to themselves as potential participants or directed to others for example future populations or communities. It can be seen then that both parties involved in the interaction are using each other for some form of gain. This instrumental use however does not mean that either party does not give the other party the respect owed to them. Researchers/sponsors use trial participants as a means to an end and at the same time treat them as ends in themselves. The same can be said regarding the trial participants, they use the researchers/sponsors as a means to an end but at the same time treat them as ends in themselves. Hence there is no instrumental use within the interaction.

If there is no instrumental use of the participants, then can that same interaction be degrading to the potential participants? The use of participants as means by the researcher/sponsor is not in and of itself degrading. If it were then the use of any person with the aim of benefit to oneself would be labelled as being degrading. For example the use of a plumber would be instrumental and degrading since he is hired with the aim of benefit to the person hiring him. In order for us to prove that an instrumental use is degrading we need to prove that the party being used is disrespected or believed to hold lower moral worth than the other party. Through the process of hiring the plumber or recruiting participants into a trial, the individuals being used may still be valued for who they are. This mutual use of others through their consent does not represent disrespect to them as rational beings. From a Kantian perspective one can only demean or degrade another person if he

displays lack of respect for their equal moral worth. He does not however view the interactions stemming from the inequalities of power as lacking in respect for the person as a moral being. In order for a person to degrade another, that person has to view the person being used as holding lower moral worth than others. In other words we need to prove that the researchers/sponsors view the potential trial participants from developing countries as having lower moral worth than other potential participants from more developed countries. This may be related to their race, ethnic background, or social status for example. Therefore, interactions are degrading not because of the existing imbalance of power between the researchers/sponsors and the participants or their communities or because of the mere benefit to the researchers/sponsors from that interaction. Hence for us to label these interactions as degrading we need to prove that the participants from developing countries are viewed as having lower moral worth than participants from more developed parts of the world.

Several points need to be outlined which may be seen as reasons to support the argument that researches/sponsors degrade trial participants. To begin with there is the issue of shift of trials which would never receive approval within developed countries to developing countries. Does the fact that these types of trials would never be approved within developed countries mean that the trials are degrading to the participants from developing countries? Different circumstances exist within developing and developed countries which may sometimes force the researchers/sponsors to make certain alterations to the trial designs to better serve the communities within developing countries and to ensure social value. Furthermore the lack of regulations within some developing countries regarding

clinical trials or the possibility of recruitment of the required number of participants within a shorter period of time due to the high prevalence of a given condition does not lead to that conclusion either.

Secondly, if we accept that certain circumstances may justify alteration to trial proposals to aid in answering the trial questions, can we say that if the trial results are intended for distant populations, other than those recruited into the trial, that the interaction is degrading to those participants from developing countries. If we did, then all research involving human participants will be labelled as degrading since research in general is performed for the benefit of future patients and populations rather than the direct benefit to the trial participants. All research aims at generating generalizable knowledge for the benefit of future populations regardless of where they reside. The results of trials performed in developed countries are sometimes applied in clinical practice within developing countries. Does this mean that the participants from developed countries were degraded? Certainly not, these participants may benefit from the trial results as well as future populations or people residing within other countries or even continents. However, given the vulnerable status of populations within developing countries, their enrolment within trials has to be justified. It has to be ensured that their recruitment into the trial is necessary in order to answer the research question and that they are not merely recruited for the convenience of the researchers/sponsors. Vulnerable populations in general should not be recruited into trials except where there is an anticipated benefit to them at the end of the trial. There should be some anticipated benefit directed either towards them or their communities.

Degradation and the view of participants as holding lower moral value can be seen through the failure of the researchers/sponsors in obtaining consent from the potential participants or if consent is obtained through manipulation, deception, or coercion as has been discussed in chapter two. If we take the Surfaxin trial as an example, we can see that a placebo controlled trial would never be approved in more developed countries in the first place due to the availability of many alternative effective agents for the treatment of ARDS. The setting within Bolivia is different. There are no treatment options available making the use of placebo controlled trial a valid option for the researchers/sponsors. Furthermore, the location of the trial was selected based on the high prevalence of the disease within that setting, a point which we have stated earlier does not mean that the participants recruited into the trial are being degraded. In addition, there is no reason for us to believe that the researchers/sponsors view the trial participants' as holding lower moral value. Informed consent has been obtained from the trial participants' guardians, a procedure which shows that the trial participants were respected as rational moral agents. There has to be another aspect which prevents us from approving this kind of a trial. This will be further discussed when we talk about social value.

Kant's universal law formulation:

Further along the Kantian line of argumentation, the universal law is used to argue against the instrumental use of people. The first of Kant's categorical imperatives is the universal law formulation which states:

“Act only according to the maxim by which you can at the same time will that it should become a universal law” (Rachels, 1999: 133)

What Kant is saying is that we should act through a maxim where we accept that our actions become the law of nature. The real test to Kant was whether we could will for our actions to become a law of nature which would be applied to oneself as well as others. The best example used usually to clarify this concept is that of deception. In order for deception to work, the universal law has to be that of honesty. People fall for deceptive proposals because they assume that the person requesting any given action is honest. If they knew beforehand that he was deceiving them, if deception was a universal law, they would not agree to the interaction and refuse the requested proposal. Therefore if deception became a universal law it would be self-defeating. However, this line of thought fails before it is even initiated since we have stated earlier that there is no instrumental use of trial participants through the alterations of trial proposals to better suit the local setting. We have also argued in the earlier section that the mutual use of the researchers/sponsors to trial participants and vice versa does not mean that the researchers/sponsors are using the participants instrumentally. Research itself is willed to be a universal law where certain people are exposed to risk for the benefit of future populations. Yet this line of thought does not justify the prevention of mutually advantageous consensual interactions between the researchers/sponsors and the trial participants.

Paternalism:

Paternalistic prohibition of certain interactions stems from the concept of protecting participants from entering into interactions which do not advance their own interests. Although this may apply in some situations it would be difficult to justify prohibiting all advantageous interaction based on paternalism alone. For example mutually advantageous exploitative interactions where the participants actually stand to benefit even if they are exploited cannot be justifiably prohibited based on paternalism alone.

Prophylactic argument:

This argument is not one of the strong arguments for the prohibition of mutually advantageous exploitative interactions in my opinion. It is based on the idea that not all interactions between the researchers and participants are beneficial to the participants and in some cases informed consent may not be “informed” or valid. Therefore, it would be better to prohibit all such interactions in order to prevent the participants from being exposed to harm. Its aim is to prevent exploitative interactions. The weakness in this argumentation is that it does not actually justify the prohibition of mutually advantageous exploitative interactions. It calls for the prohibition of all interactions because of the risk of harm that these interactions potentially hold within them. It does not concentrate on the prohibition of interactions that actually cause harm and permit those that do not. This is important to state since we are trying to justify the prohibition of interactions which are in fact going to benefit the participants. If all interactions between potential participants and researchers should be prohibited based on the concept of potential harm to the participants

then no clinical trial, starting from phase I trials, would be approved since all trials at all levels entail some sort of risk to the participants. Furthermore, the assessment of the acceptability of harm should be done by the potential participants and not external members. This specific point has already been discussed earlier in this chapter and the assessment of the acceptability of risk should be left in the hands of the potential participants.

Strategic intervention:

This concept is presented by Hawkins and Emanuel as well as Wertheimer. The basic idea behind the strategic intervention is the promotion of non-exploitative interactions though the prohibition of exploitative ones. Wertheimer states:

"Whereas paternalistic interventions override the individual's preferences, strategic interventions serve to help enable a person get the result that she already prefers but cannot obtain without such intervention." (Wertheimer, 2010: 216)

In such cases, the aim of prohibiting, even mutually advantageous exploitative interactions is to allow for a non-exploitative interaction to take place. By prohibiting exploitative interactions between the researchers/sponsors and participants, we instead encourage researchers to enter into non-exploitative interactions with the participants. Although we have stated earlier that the redirection of trial results to other populations is not the problem per se, the health care settings within developing countries, how health is valued, and the spread of life shortening illnesses within developing countries make certain exceptions necessary.

Health is considered one of the basic human goods without which people cannot live a thriving life. To this effect Rawls states:

“primary goods..... are things which it is supposed a rational man wants whatever else he wants With more of these goods men can generally be assured of greater success in carrying out their intentions and advancing their ends, whatever these ends may be” (Rawls, 1999: 79)

Others, like Daniels argue that health becomes a special kind of good as a result of the unfair distribution of healthcare services and the importance of health to individuals (Daniels, 1985). Therefore, someone’s need for treatment for an illness is the same regardless of where they reside. Given this classification of health as a special kind of good and the devastating illnesses causing unnecessary preventable deaths within developing countries, it is better to focus trials performed within these settings on the needs of those populations and on finding treatments for those illnesses. Hence, the argument becomes the need to maximise the benefits to those worse off in the interaction.

Based on this approach trials are usually divided into responsive and non-responsive trials. Non-responsive trials are those which recruit trial participants from developing countries with the intention of redirecting and applying the benefits of the trial to other better off countries. Responsive trials are those which recruit participants from a given location with the aim of benefiting these participants or future populations within that same geographical location or those who suffer from the same medical condition. I think there are two different

issues that need to be clearly distinguished from each other in order for the assessment to be precise: the degradation of the participants and the social value of the trial. Social value refers to the value of the trial to the community or the population which the trial is recruiting from. Hence a trial may be defined as being responsive if it has social value and non-responsive if no social value is anticipated. On the other hand degradation, as we have discussed earlier, refers to the way that the moral worth of the participants is viewed.

Responsive trials are performed with considerations of the needs of the trial participants and with the goal of benefiting them in the end. For example the AZT trial was performed in order to find out the effectiveness of shorter courses of ACTG 076 due to the very high incidence rates of this devastating illness within the Sub-Saharan African region. The participants within the trial were recruited into the trial with the aim of benefiting them as well as their communities at the same time therefore it was a responsive trial. One could anticipate an argument against the AZT trial to mention that since the trial failed to make available the intervention to the population recruited at the end of the trial, then it failed to fulfil its social value perspective. This argument is not a valid one. The aim of the trial at the time of proposal was to find a less costly, shorter course of the intervention which would be affordable to the population being investigated for the prevention of maternal to foetal transmission of HIV infection and has reached that goal. It lowered the cost of the intervention significantly from \$800 per person to \$80 per person. By achieving this goal, the trial did answer its research question and fulfilled its social value goal. The fact that the local government within some developing countries still considered this cost to be too expensive compared to its expenditure does not mean that the trial has failed in its responsiveness.

from a social value perspective. The failure from the government to afford the intervention comes from a financial point of view at a post-trial stage. Furthermore, referring back to the analysis of the social value and its assessment from an ex-ante perspective, we can see that the researchers/sponsors did not know that even after lowering the cost of the treatment that the cost would still be too high for the local government. This was not known to the researchers at the beginning of the trial. Hence it can be seen that there may be other reasons which could render responsive trials unable to meet their goals or to fail in other aspects for example when the requirements of informed consent are not met. From a social value perspective, the AZT trial is a responsive trial.

On the other hand the Surfaxin trial aimed to prove the effectiveness of a new agent for the treatment of a life threatening illness affecting infants without any consideration to the improvement of the health care status within Bolivia. The trial did not aim to make available a treatment for this life threatening condition within that setting, nor did it aim at lowering the high cost attached to these interventions in order to aid the local authorities to afford these interventions and therefore make them available to their populations. The whole benefit of the trial was anticipated to be directed to future patients within the better off, more developed countries. Although I have argued that this does not count as an act which would degrade the participants within the trial, the trial's failure to consider the social value of the population leads us to prevent it in order to encourage better more socially valuable trials.

Hence the aim of the strategic intervention is the prevention of the socially valueless trials in order to promote socially valuable ones. It is the lack of attention of the trial sponsors to the

devastating illnesses that are so widely spread within some developing countries that lead us to argue that there has to be a focus on the social value of these trials to the specific population within these developing countries. We need to prevent trials recruiting participants from developing countries with no social benefit in order to encourage trials that have the potential of social value.

To better understand the strategic intervention, let us consider Wertheimer's scenario assuming that placebo-controlled trials cost less than active-controlled trials and furthermore that trials performed within developing countries are less expensive than those carried out within the United States which may be due to several factors one of which is the prevalence of the illness within that region. In general, four options are available to the researchers:

1. A placebo-controlled trial in the US
2. A placebo-controlled trial in a developing country
3. An active-controlled trial in US
4. An active-controlled trial in a developing country

Given that option (1) rarely becomes available to researchers because placebo-controlled trials are not allowed unless no other method of treatment exists, three other options are left. The performance of placebo-controlled trials within developing countries, option (2), may be acceptable in certain circumstances and cannot be placed under the category of exploitative interactions blindly. Given the non-existence of treatments for some of the illnesses devastating some of these regions, it may become necessary to perform a placebo-controlled trial. The distinction of whether such trials are exploitative (or not) depends on

their social value. For example, going back to the Surfaxin trial, the use of placebo is not problematic because of the use of the placebo itself instead of an active agent given that no alternative treatments exist within the trial setting within Bolivia. The problem with the trial is the lack of value the trial is anticipated to provide to the society. The target population of the post-trial benefits was that within developed countries, there was never any intention of performing the trial in Bolivia with the aim of benefiting that society or any other developing countries where no treatments are available for this life threatening condition. Hence, placebo-controlled trials may be classified as exploitative depending on the social value of the trial. Active-controlled trials, option (3) and (4), may be seen as being balanced since they both compare the tested agent with an active one. Between these two options, Wertheimer argues that researchers/sponsors will choose to do the trial in the United States i.e. they will choose option (3). I disagree with Wertheimer. Given the market driven nature of performance of trials especially by for-profit sponsors, I think that researchers/sponsors will choose option (4) and opt to do the trial in developing countries due to the lower cost of running the trial there. However, given that no treatment options are available within developing countries health care settings, the use of active-controlled trials will cause more problems especially if the more expensive agent turns out to be more effective. We have mentioned earlier that among the reasons for the in-availability of effective treatments within developing countries is their high cost as is the case with the AZT trial. Less expensive effective treatments need to be made available. Choosing option (4) is not practical within developing countries unless a treatment modality is in fact available within that setting.

Therefore we have three options: placebo-controlled trial (with social value) in a developing country, active-controlled trial in the United States, and active-controlled trial in a developing country. In addition, given that placebo-controlled trials are less costly than active-controlled trials, I argue that researchers/sponsors will choose option (2). The strategic intervention requires us to prohibit exploitative interaction such as socially invaluable placebo-controlled trials in developing countries.

On the other hand, if we assume that the cost of carrying out a trial in the United States is less expensive than in developing countries the situation changes. The options available to researchers will again be the four presented above. This time however, option (1) is not plausible because placebo-controlled trials are not allowed in the United States when other proven medications for the treatment of a specific condition are already available. We are once again left with the same three options and I would argue that researchers would still choose to perform their trials within developing countries, option (2), since placebo-controlled trials cost less than active-controlled trials. Applying the strategic intervention here means that we prevent socially valueless placebo-controlled trials within developing countries in order to promote socially valuable placebo-controlled trials. This rationale follows the strategic intervention as presented by Wertheimer. It could be anticipated that if the strategic intervention is applied then some researchers/sponsors will simply take the trial somewhere else. Should this happen developing countries populations will lose the opportunity to benefit from the trial. Although this may be true in some cases, the aim of the strategic intervention is to prohibit interactions which are exploitative and promote those which are less exploitative. An example which is used by Hawkins and Emanuel will help

clarify the issue. Labour unions prohibit the agreement of individual labourers to low wages because they want to promote better wages for all labourers (Hawkins and Emanuel, 2008). Hence, if we apply the same principle to clinical trials within developing countries and all mutually advantageous consensual socially valueless interactions are prohibited, this will promote better option i.e. non-exploitative, socially valuable interaction.

Exploitation of communities:

A community is defined as a group of individuals who share some common features like culture, language, geographical location, religion, political authority, disease etc., and who regard themselves as part of the same group, distinct from others who do not share these features (Gbadegesin and Wendler, 2006). However, the characteristics that are most commonly used to recruit communities into clinical trials most include culture, political authority, shared resources, and self-identification (Weijer and Emanuel, 2000).

Like individuals, communities may be exploited; however the exploitation of communities differs from that of individuals (Gbadegesin and Wendler, 2006). To begin with communities cannot be exploited through the exploitation of their individual members for example; the exploitation of individual participants from Bolivia in the Surfaxin trial does not mean that the community as a whole has been exploited. Secondly, the interaction itself has to rely on the community's resources. These resources may be in the form of physical resources such as health care facilities or non-physical resources such as the use of the approval processes that exist within the community. Furthermore, we have to focus on the reasons for the selection

of certain communities for example certain cultural beliefs or characteristics within that community, existing health features, or due to simple discriminatory behaviours.

So how do we protect these communities as a whole from exploitation? All the criteria that make interactions unfair to individual participants from an outcome perspective also apply to their communities. The same imbalance of power between the researchers and the communities exists as mentioned earlier and they may be unable to refuse certain interactions based on funds provided in other areas. The interaction itself may have one of three effects on the communities. In this framework communities become regarded as harmed, benefited, or unaffected through their interaction with the researchers/sponsors.

No Effect:

The interaction between the communities and researchers/sponsors may have no effect on the community itself especially if the researchers/sponsors do not utilize any resources from the community. However, the interaction between the researchers/sponsors and the communities rarely has no effect whatsoever on the community. Some community resources may be utilized by the research team such as health care facilities, laboratories, or professionals. Hence, we cannot say that the community interaction with the researchers/sponsors will have absolutely no effect on that community.

Harmful effects:

The community may be harmed by its interaction with researchers/sponsors through two possible routes. It may be harmed through the utilization of existing community resources such as existing clinics and through the use of its health care providers. In some cases, this

harm may have a big impact on the health care services of the community especially where these resources are scarce in the first place. However, as we stated earlier, the acceptability of harm should be assessed by the community itself or representatives from that community just like potential participants are required to assess the acceptability of the potential harms of the trial. Furthermore, the analysis of harm to the community has to go through the net-risk analysis as was done for the individual participants from identification of the net-risk interventions, assessment of net-risk interventions, and assessment of cumulative net-risk. The assessment though has to focus on the harms to the community rather than those anticipated for individual participants.

1. Identifying the net-risk interventions:

Once again the first step required us to identify individual interventions within the proposed trial, assess their risk-benefit profile, and compare them with the available alternatives outside the scope of the trial. If we return to the AZT trial and the Surfaxin trial, the interventions available within the trials include an active agent (AZT or Surfaxin) and placebo. The use of either of these interventions may harm the community through the use of its resources, health care facilities, and health care providers. The risk however is not high given that no treatment option is available outside the scope of the trial. Another form of harm to the community could come to life through more expenditures for the treatment of the potential participants should the interventions not prove effective. However this risk does not exceed the risks that exist outside the scope of the trial. The anticipated benefits to the community include the training of its health care providers and in the case of the AZT trial, the availability of a more affordable treatment option for a disease that devastates the

community and its members. Hence both trials do not have a net-risk given that the trial is at least as favourable to the community as the available intervention prior to its interaction with the researchers.

2. Assess the net-risk interventions:

When we shift to the social value of the trials, different outcomes come to life. The AZT trial has potential social value through the lowering of the cost of intervention used for the treatment of an illness that is affecting large numbers of its populations and which causes unnecessary annual deaths. This potential benefit outweighs the risks the community is expected to shoulder through its participation within the trial. On the other hand, the Surfaxin trial proposed no social value and hence has a net-risk.

3. Assess the net cumulative risks:

The cumulative risk of the AZT as well as the Surfaxin trials is justified through the assessment of its risk. The cumulative risks equate to those risks outside the boundaries of the trial.

Benefit:

A community may enter into an interaction with the researcher while anticipating different types of benefits such as the improvement of existing health care facilities or the establishment of new ones, the gain of medical equipment, or the training of health care providers. The community may also anticipate saving health care costs due to the lowering of the cost of some of the intervention or the improved health of the individuals within that

community which leads to reduced expenditure. Despite the existence of benefit to the community, exploitation may still exist within the interaction of the researchers/sponsors if the community it is interacting with or certain features within that community are viewed to have lower moral value than other communities. Furthermore, it is important to reemphasize that the benefit to the communities is assessed based on whether the community receives a fair share of the benefits at the end of the interaction compared to those gained by the exploiter. This point will be the focus of chapter five when we discuss post-trial benefits.

Conclusion:

Exploitation is a term that tends to be used rather loosely to describe actions and behaviours that we feel are immoral. I focused the analysis in this chapter on outcome unfairness which assessed exploitation based on the end result and how it affects the parties involved within the interaction. The chapter presented a focus on outcome fairness from both the individual potential participant and community's perspectives. All possible outcomes were considered including no effect, benefits, and harms. A tool for a detailed assessment of harm was presented and the delegation of assessment of acceptability of these harms was given to the potential participants or communities themselves. Furthermore, the chapter presented arguments for the justification of the prohibition of mutually advantageous consensual exploitative interactions.

The interaction between the participants and researchers/sponsors may affect both parties but because the participants are the ones considered more vulnerable within that interaction, a much larger proportion of the discussion has focussed on them. As with any

interaction between two parties, the participants may not be affected at all by that interaction, they may be harmed by it, or they may in fact benefit from their interaction with the researchers/sponsors from an ex-ante perspective.

However, even when considering the outcome of an interaction, I have suggested that the assessment of harm and its acceptability within an interaction should be done by the person or community being exposed to the harm and not by others. Certain individuals may accept high levels of risk whereas others may not accept entering into interaction with even minimal risk. I have also argued that mutually advantageous interaction may be prohibited even if fully informed consent is provided by the participants themselves. My argument to support this prohibition relies on one main concept: the strategic intervention. This approach strives to promote non-exploitative interaction through the prohibition of exploitative ones. Through the arguments presented, we have concluded that instrumental utilization and Kant's universal law do not justify the prevention of mutually advantageous consensual interactions or clinical trials given that the whole aim of the performance of clinical trials is the generation of generalizable knowledge for the benefit of future patients or populations. It has also been argued that just like individual participants, communities may become exploited through the interaction with the researcher/sponsor. I have argued that there is no instrumental use within clinical trials as both participants and researchers/sponsors use each other mutually, each to enhance their own benefit. Furthermore I argued that in order for degradation to be present, we need to show that the researchers view trial participants as having lower moral worth than participants from developed countries. This did not become

evident through argumentation as due respect was given to participants through the process of informed consent and respect for the decisions of the participants.

The next chapter discusses the post-trial stage and what is owed to trial participants (if anything) by the researchers. The chapter will also look at the issue of a fair share of the benefits and how it can be achieved.

Chapter Four: Post-Trial Benefits

Introduction:

The chapter will focus on benefits at the end of the trial and how to ensure that each party involved within the interaction benefits fairly. The arguments will conclude that post-trial access or reasonable availability takes on a very limited approach to the anticipated benefits to trial participants and their communities. A more productive way would be to adopt a post-trial benefit approach. This approach takes into consideration a much broader view about post-trial benefits to trial participants and their communities which include direct, collateral, and aspirational benefits. This broader view of post-trial benefit aids in the improvement of the existing circumstances within these communities. With that same purpose in mind, a global research tax is presented. This is a form of taxation which should be implemented on all for-profit industrial research sponsors performing trials within developing countries. This global research tax is implemented through the deduction of a certain percentage of sponsors' profits. This money is then directed towards improving the settings within these developing countries. The implementation of this whole improvement process should be done through a monitored and supervised process under the umbrella of either the United Nations or the World Health Organization. This supervisory role is essential to ensure that the funds obtained through the global research tax are being directed and utilized for their intended purposes.

After the trial results are obtained and the trial is terminated, the sponsors shift their focus towards marketing the intervention and making a profit, with the end result being that the proven intervention becomes available on the market (Black, 2001). From an outcome perspective of fairness we have to assess whether the parties involved within the interaction all benefit in a fair way or not. In order to do this we need to look at the different forms of benefit at the end of the trial. This chapter will focus on the kind of benefits that are generated from the trials, how they are distributed among the different parties involved, how these parties relate to each other, the kind of duties, if any, owed by each party to the other, and whether exploitation exists within such circumstances and how it may be minimized.

Benefits:

Benefit is the enhancement of the well-being of an individual. The researchers/sponsors benefit is most commonly represented in monetary terms. Global pharmaceutical sales reached \$712 billion in 2007 (Petryna, 2009: 2). Sponsors perform trials to test their new agents, evaluate old agents for a new purpose, obtain or extend patency rights for an intervention, and ultimately make a profit. These profit driven industries strive to reap financial gain through marketing products. Achieving rights to market the product however, can only happen once the sponsors have secured approval from the appropriate local authorities.

Investigators also stand to benefit from the trial results in many other ways. They can become famous by publishing the results, receive academic recognition for their work that

leads to pay raises, obtaining an academic title, and perhaps entertain monetary rewards or other forms of rewards from the sponsors. In the United States alone about one-quarter of US researchers reported accepting significant rewards from pharmaceutical industries including financial rewards, sponsored speaking engagements, positions on advisory boards and equity holdings (Boyd and Bero, 2000). In discussing potential beneficiaries however, we have left out the most important party involved in the trial, the people who made the trial possible, the participants, their communities, and the beneficiaries of the drug once marketed.

Benefits to trial participants:

Benefit to trial participants can be evaluated from different perspectives. From a broad perspective, benefit can incorporate several forms that the trial participants may enjoy. King identifies three broad categories of benefit arising from research (King, 2000: 333). The first one is the direct benefits that the trial participants experience due to the intervention being received during the trial. The second benefit, which she calls collateral benefit, refers to the benefit gained even if a participant is allocated in the placebo arm of the trial and does not receive the active intervention. These collateral benefits include medical examinations as well as medical tests that the participants have to go through which may lead to an improvement in their health status and may not be available to the trial participants outside the scope of the trial. The third category of benefit is what King calls aspirational benefit which is experienced by the community and future patients from the results of the study. The alternative route of viewing benefits to trial participants takes on a very narrow view of

the issue and usually focus on the direct benefits to the participants (Lurie & Wolfe, 1997: 337) or the increase in collateral benefit (Shapiro and Benatar, 2005: 31). When considering direct benefit the discussions usually focus on the provision of the effective treatment to the trial participants once the trial is terminated. This is also known as post-trial access. For the purposes of the discussions in this thesis, the benefit that participants receive will be discussed under two broad headings: post-trial access and post-trial benefit. Each of these perspectives will be presented separately.

Post-trial access:

Post-trial access refers to providing the proven intervention to trial participants once the study has ended. This approach is intended to assure that trial participants are not exploited. This is also referred to within some documents as reasonable availability. This section will discuss the effectiveness of this approach and will further analyse, and show the weakness of the arguments used to support it.

Reasonable availability:

Some international guidelines, view a reasonable availability approach as the best way of ensuring that participants have post-trial access to the proven intervention and hence ensuring benefit to the trial participants. The Council for International Organizations of Medical Sciences (CIOMS) states:

"In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It

should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health. (CIOMS, 2002: 12)

Some believe that adopting the reasonable availability approach by giving the proven intervention to research participants represents the sole route for minimizing exploitation and benefiting trial participants (Hawkins and Emanuel, 2008). Although this approach may reduce instrumental use of trial participants and likelihood of exploitation by ensuring that trial participants benefit at the end of the trial, or at least receive some proportion of the benefit, this approach has its own limitations. Furthermore the approach is not a practical one as will be shown below.

The main limitation of reasonable availability is its focus that benefit to potential participants only exists through the provision of a proven intervention at the end of the trial. Although this may be a form of assurance that trial participants receive some form of benefit at the end of the trial, that very narrow view of benefit is the source of limitation of the argument itself. Assuming that procedural fairness has been ensured through the process of informed consent, and assuming as well that the participants know the duration and terms of participation within the trial, then it has to be assumed that the agreement of the participants to be enrolled into the trial was based on the knowledge that they will not receive the proven intervention at the end of the trial. Although it is true that through the provision of the proven intervention we may be closer to assuring outcome fairness since the participants will actually share with the researchers/sponsors some of the benefits of the

trial, the weakness of the reasonable availability argument lies much deeper than this superficial layer. Problems with the reasonable availability approach surface once we take a closer look at the practicality and feasibility of its application.

The first argument against reasonable availability uses the narrow view of benefit to prove the difficulty with the application of this approach. Reasonable availability depends on demonstrated product efficacy. This approach can only work in the context of positive phase III trials where one intervention is proven more effective than another existing intervention or placebo. If reasonable availability views non-exploitation of trial participants only through the provision of the proven intervention, this means that individuals who participate in positive phase III trials where an intervention proves to be effective may be treated fairly by the researchers/sponsors as they will be provided with the proven intervention. On the other hand many other trial participants including phase I, phase II and negative phase III trial participants gain no benefit whatsoever and are therefore exploited from an outcome perspective because no proven intervention can be provided to the trial participants after the trial has come to an end. This approach is problematic since positive outcome from phase III trials showing effectiveness of an agent occurs rather infrequently (Djulbegovic et al., 2000, Chalmers, 1997). Therefore, focussing solely on the provision of the proven intervention means we are depriving negative phase III trial participants of all other forms of trial benefit. The same line of argumentation would be difficult to defend if a trial did not end with proving one arm of the trial as being superior to the others. In these circumstances, the participants will be left without the provision of a proven intervention and will therefore, according to the argument presented through reasonable availability, be exploited. This

inability to provide the proven intervention however came about through no fault of the researchers/sponsors. There is simply no proven intervention to be provided to the participants. Furthermore, and even if we reserve reasonable availability for phase III trials, there is no guarantee of a benefit in the form required by reasonable availability. If equipoise truly exists at the beginning of any trial, then there is no way of knowing which arm of the trial will prove effective (Freedman, 1987). The whole aim of the trial is to assess the effectiveness of the tested intervention against other proven interventions or placebo. In some cases this effectiveness may not be proven and there may be no proven intervention to be provided to the trial participants. How can we apply reasonable availability when the trial agent proves ineffective? This approach requires ensured access to the proven product, yet in negative phase III trials none exists.

I think that because of this very narrow concept regarding benefit to the trial participants, the labelling of exploitation has been attached to many trials where a proven intervention has not been provided to the participants once the trial has ended. Reasonable availability sees provision of the proven intervention to the trial participants as the only way for the assurance of non-exploitation or fairness to the trial participants.

This argument is not entirely true though since phase I and II participants may gain other forms of benefit which may be worth more to them than the provision of the proven intervention but reasonable availability does not recognize these forms. In reality benefit to trial participants could come in different forms. The knowledge gained from phase I and II trials does not come in the form of an agent that can be marketed or be made available to the public. Yet it cannot be denied that the knowledge gained through these trials and

information generated is very valuable and may lead to the initiation of further research which may in the end come in the form of a proven intervention. However, the immediate participants of these early trials do not gain access to this proven intervention. Reasonable availability therefore excuses phase I and II trial sponsors from providing benefits to the participants due to the absence of a proven intervention. Those individuals recruited as phase I, II, and negative phase III trials, who helped sponsors collect the information needed for phase III trials and with advancing our knowledge do not stand to gain any benefit whatsoever after the trial has ended.

Another weakness to the demand for post-trial access is the assumption that the approval of the placement of any given proven intervention on the market lies within the hands of the researchers/sponsors. This assumption fails to recognize the reality of the complicated and lengthy process that the proven agent has to go through prior to it being approved by the appropriate authorities. In industrialized countries, the pharmaceutical company applies through the appropriate authority to register their product and get the green light for marketing their agent once a clinical trial has ended. This process can take some time because the regulatory authority has to review the trial results and judge whether claims made by the sponsor about the effectiveness of the intervention hold. Sponsors can expect delays from the time the results of the trial are obtained until the time the intervention actually goes to market for several reasons. In some cases, the regulatory authority may not find the results convincing based on statistical data, and as a result ask the sponsors to confirm the results through another clinical trial. However, this should be an infrequent incident especially if due care was exercised through the approval process and the scientific

validity was scrutinised. Secondly, the results of the clinical trial may be inconclusive. The intervention has to show either superiority over placebo, the preferred method of comparison by many sponsoring agencies, or at least prove to be as effective as other established interventions for the same medical condition before the product can be permitted to be placed on the market. When the results are inconclusive, the regulatory authority may insist upon the sponsor carrying out yet another round of testing in perhaps a different location, meaning that the participants have to await new test results before being given post-trial access to the required intervention. Therefore, to insist upon researchers/sponsors to guarantee the availability of any intervention prior to its approval may prove difficult in cases where the official agency responsible for approving interventions refuses to authorize the agent. This is a problem faced by sponsors in developed countries as well as developing countries.

Similarly, sponsors do not have the authority to instruct ministries of health in developing countries, or any other location for that matter, to make a specific intervention part of their public health plan. This is a decision that can only be made by the appropriate authorities depending on societal needs and future plans. The most a sponsor can do is inform the appropriate authorities about the intervention and guide them to its appropriate use. The final decision has to come from the developing country itself. The AZT trial is the best example for the failure of the assurance of post-trial access as well as the inability of the researchers/sponsors to force the local authorities to provide the proven intervention to their populations.

There are several other arguments usually used to defend post-trial access. These include the expectations of the trial participants, abandonments, prevention of instrumental use, and justice of reciprocity. Each of these will be discussed separately.

Expectations of participants:

In defence of post-trial access, it is sometimes argued that trial participants expect continued access to proven intervention once the trial has ended. Hence if that expectation is not fulfilled the interaction is labelled as being unfair or exploitative. This claim can hardly be considered as a general rule since trial participants may base their expectation on unrealistic or false information or misconceptions. To show the evidence of such expectations let us consider an example of a multicentre trial testing a drug for the treatment of Parkinson's disease (Amgen case). This trial was terminated by the sponsoring company for safety reasons despite the fact that some patients reported improvements in their condition (Saver 2009). The termination of the trial was justified by the researchers to be due to safety reasons. The participants launched a lawsuit against the company to demand continued provision of the intervention by the manufacturer of the tested agent.

The expectation of the participants regarding the provision of the proven intervention is not valid for two reasons. The first one relates to the consent of the trial participants to enrol into the trial with prior knowledge regarding the expected period of participation and the provision of interventions once the trial has ended as discussed earlier in chapter three. To ensure that the participants are not exploited from a procedural perspective, the terms of the moral contract between the participants and the researchers/sponsors have to be very clear from the beginning regarding the provision of the proven intervention once the trial has

ended. This approach may minimize the expectations of the participants regarding the continuation of the provision of medical interventions after the end of the trial.

The second and perhaps more difficult factor relating to the expectation of the trial participants to receive continued access to interventions relates to the mistaken equation between trials and clinical care. Participants may believe that their participation in trials automatically qualifies them to receive the proven intervention. This of course is a false impression or misconception held by some. Confusion about the nature of the researcher-participant relationship in comparison to the physician-patient relationship represents the other form of misconception leading to false expectations by participants. This form of therapeutic misconception has already been discussed in chapter two and hence will not be repeated here. Suffice it to say here that the two roles of physicians and researchers do not have the same goal nor are the same duties owed by the physicians and the researchers to the patients and trial participants respectively.

Researchers however do owe their participants the duty to ensure their informed and valid consent is provided as well as ensuring their safety throughout the trial. Relating more to outcome unfairness which is the focus of the discussion, expectations of the participants or the sponsors alike do not qualify as an argument for or against the provision of the proven interventions. If participants expect to receive a certain level or type of benefit especially if clear information has been provided to them through the communication process with the researchers and their team, the fulfilment of that expectation does not mean that the interaction between the researcher and the participants is a fair one. Furthermore, the expectation or demand of the participants may be based falsely on the principle of

autonomy. Participants may believe that one of the elements of their freedom is to make such demands. However even in clinical settings, autonomy is not absolute and may be restricted under certain circumstances. Situations where the autonomy of individuals may be restricted include for example situations where their demands are based on misconceptions, impose risk on others, or the demands are unrealistic. Hence expectations of trial participants do not form a firm basis for the demand of post-trial access.

Abandonment:

According to this view, researchers abandon their participants once they have finalized their trial and obtained their needed results. The trial participants therefore sustain loss because they no longer receive the active agent. Furthermore, the trial participants lose the extensive medical services and follow-up which they enjoyed during the trial period.

The abandonment argument fails to recognize two points, the first is that the loss the participants allegedly suffer from is not something imposed by the researchers, but rather arises naturally when allowing participants to return to their original state prior to their participation within the trial. Although this initial state may be inferior to the participant status within the trial, it does not come about as a direct result of the researchers' actions. The researchers do not make the participants worse off. Rather, the circumstances surrounding the trial populations cause this reversion to their initial state. Furthermore, there are several other kinds of benefits which the participants may gain at the end of the trial other than the proven intervention. The improvement of the status of the trial participants may come about regardless of the provision of the proven interventions. Improved local health care services and training of local health care providers may also lead

indirectly to the improvement in the health status of the participants. Hence researchers may provide alternative options at the end of the trial which may indirectly improve the health of the participants.

The abandonment argument also fails to recognise that researchers and participants have entered into a moral contract with each other. This contract states that the trial participant agrees to enrol into a trial and receive an intervention associated with one of the trial arms for a specified period of time. At the end of this period, the moral contract or relationship between the two parties ends. The participants' informed valid consent shows that they have chosen to enrol with a knowledge of all that will happen at the end of the trial. This brings the issue of procedural fairness into the focus of the argument once again. The simple obtaining of the signature of the participants on a piece of paper is not the goal of procedural fairness. Rather it is the quality of the information being presented to the participants, the communication between them and the researchers, and their comprehension of that information is of importance here. The research team needs to disclose the duration of participation to potential participants at the outset within the information sheets and emphasize this information through the communications session. It has also been argued in chapter two that the level of comprehension of information has to be assessed by the researchers prior to the enrolment of the participants into the trial. If this is ensured, the ending of the contract also means the end of the relationship between participant and researcher and not abandonment.

Admittedly, there may be instances where trial participants agree to the enrolment into a trial despite the fact that they know they are being exploited i.e. mutually advantageous

consensual exploitation. This may be linked to two issues, the first one relates to the issue of the agreement of trial participants to be enrolled into the trial due to the external circumstances that they live within. However, I have argued in chapter two in relation to procedural fairness that despite of these existing factors within the environment where the trial participants live within, this fact alone does not mean that they did not understand the information being presented to them, nor does it mean that their agreement was irrational or non-voluntary. Secondly, I have argued in chapter three that despite the fact that exploitation may in some circumstances be agreed to by the potential participants; it does not mean that the particular interaction should be allowed. However these arguments related more to the social value of the trial rather than focusing on the consent of the participants. Hence, this argument will not be further discussed here as I do not see it as having an implication on the discussion at hand.

When the demands are made for information sheets to contain certain information and for researchers to ensure proper communication and the understanding of that information by the potential participants; it cannot be argued at the same time that the researchers/sponsors should continue to provide the proven intervention after the designated time frame. Arguing that the researchers/sponsors should continue to provide the proven intervention at the end of the trial places unfair demands on the researchers/sponsors. Researchers/sponsors enter into a relationship with the trial participants based on the same terms that the participants have agreed to. They are required to perform certain duties within a specific period of time. To demand that they extend the duration of their commitment and provision of interventions for the mere reason that the

participants feel abandoned at the end of the trial is unfounded. Although the researchers/sponsors are the more powerful within the interaction, placing unreasonable demands on them is also unfair and may be labelled as being exploitative of the researchers/sponsors.

Furthermore, and assuming that the abandonment argument holds, post-trial access demands should be directed at the researchers or their institutions because they form one of the contracting parties whereas in reality, the researchers as well as institutions do not have the power, authority, or financial capability to supply trial participants with the proven intervention. The only authority capable of supplying the proven intervention is the sponsor of the trial or the pharmaceutical company. Yet, trial participants have no rightful claim to receiving proven intervention directly from the pharmaceutical company because in reality participants never enter into a legally valid contract with the sponsoring party. This specific point was challenged in the United States courts through the Amgen case which was presented earlier (Saver, 2009). After the termination of the trial for safety reasons, the participants launched a lawsuit against the company to demand continued supply of the intervention. Their claim was based on promises made in the informed consent document assuring participants post-trial access. The court ruled that because no contract existed between sponsors and participants the latter could not claim access to the drug from Amgen.

“In this complex web of contractual relationships, there were, importantly, no direct agreements between Amgen and the subjects, and so the subject’s breach of contract against Amgen failed” (Saver, 2009: 422).

Therefore, the only authority capable of supplying the intervention remains outside the contract. Furthermore, the court ruled that despite promises made in the informed consent form assuring the participants about post-trial access to the proven intervention, these promises were not unconditional and subject to change in the event of trial termination for scientific reasons such as efficacy and safety. These loop holes make it almost impossible for participants to demand post-trial access from sponsors directly. This is perhaps why some international guidelines encourage the discussion and specification of post-trial benefits prior to trial approval. In addition, the participants presume receiving a continued supply of proven intervention whereas I have argued earlier that the contract between the researcher and the participant should be very clear regarding the provision of the proven intervention at the end of the trial. This presumption once again stems from confusion between the roles of the researcher and physician and misconceptions concerning the respect for autonomy. Even if we assume that physicians and researchers play similar roles, physicians are not required to give in to patients' demands, or provide unproven interventions for their patients. The respect for autonomy means respecting the choices of patients or trial participant and allowing them to choose options suitable to them. However, this freedom is not absolute and may become restricted justifiably under certain circumstances. Furthermore, the provision of post-trial access to trial participants only reinforces the misconception held by members of the public that place the physician-patient relationship at an equal level with the researcher-participant relationship.

Instrumental use:

To use someone instrumentally is to utilize them for the sole purpose of reaching one's goal without respect or regard for their own needs, or without them benefiting at the end of the interaction. To prove that researchers/sponsors use the participants instrumentally we need to prove that these points actually exist within the interaction. Although we have argued in chapter three that there is no instrumental use of participants by the researchers given that the interaction is mutually advantageous and that they both use each other in order to gain benefit, we need to focus the discussion of instrumental use here from the post-trial perspective. There are many different accounts of respect (Feinberg, 1975; Hudson, 1980). Broadly speaking, respect is owed to all people regardless of any other factors for example characteristics or social value. Perhaps the most influential discussions about respect have mainly revolved around the Kantian perspective which argues that respect is owed to persons because they are rational beings. The categorical imperative demands that we:

“Act in such a way that you treat humanity, whether in your own person or the person of any other, never simply as a means but always at the same time as an end” (Kant, 1785/1996: 4: 429).

The respect owed to those rational individuals, according to Kant, is unconditional because they have an intrinsic worth or dignity. It is because of this dignity that humans are not to be used as mere objects. The unconditional requirement for respect is built on two main features, that of their ability to determine ends and their ability to act autonomously (Wood, 1999; Korsgaard, 1996; Hill, 1997). The ability to set ends is based on the person's capability

to use rationality and reasoning to make decisions whereas their ability to act as autonomous individuals relates to their ability to make choices freely that will fit in with their future plans and therefore life.

The respect of the researchers/sponsors to the participants is represented on two main levels, prior to their enrolment into the trial and after enrolment. Prior to enrolment, participants are respected through the assurance of procedural fairness where they are provided with certain information and given the freedom to choose whether to enrol into the trial or not. After enrolment, the respect to the participants is represented in the researchers'/sponsors' respect for the confidentiality of the participants, and informing them of any adverse events that may unexpectedly occur during the clinical trial. Participants should also feel free to withdraw from the trial if needed, and should not be forced or coerced to continue their participation in the clinical trial.

The lack of benefit at the end of the interaction is perhaps the most commonly used point to support the argument of instrumental use of the trial participants. This argument focuses on the outcome fairness of the interaction between the researches/sponsors and the participants. If viewed from a post-trial access point of view, which is based on the provision of proven interventions, all other forms of benefit that the trial participants actually gain through their interaction with the researchers/sponsors are excluded. The participants of the trial receive extensive health care services and attentions only through their involvement in the trial. Other members of the community do not have access to the same level of health care services. This aspect within itself is a huge benefit to the participants and in some cases may lead to the improvement in their health status. Participants also frequently receive

continued services once the trial has ended. Otherwise stated, additional trial effects come into play which may benefit participants. Their interaction with the researchers/sponsors is not exploitative, from an outcome perspective at least, since some form of benefit does exist. Having said that, the interaction itself may still be defined as exploitative even with the benefits being provided to the trial participants as has been discussed in chapter three since some exploitative interaction may actually benefit the exploited party.

Justice of reciprocity:

The phrase “justice of reciprocity” implies that people who participate in an action deserve to benefit from it; for example, trial participants who commit their time and effort into the trial as well as their acceptance of the risks entailed within the trial should receive a fair share of the benefits that are generated from the trial.

“Each person who benefits from the contributions of others in a cooperative enterprise in which that person participates owes something to those other contributors, and they, for the same reason, owe something to these individual, but only insofar as that individual is a contributor.” (Buchanan, 1990: 229).

Reciprocity entails that benefit to both parties involved should be ensured through the distribution of the net benefit. Sponsors benefit immensely, especially in positive clinical trials but mostly in a financial manner. What we need to look at is how the participants’ collateral benefit could be labelled as being a fair share. There are several ways through which the participants of the trial may benefit and for the purposes of this section they will

be divided into monetary benefits and health benefits each of which will be presented separately.

Monetary benefit:

One way of ensuring reciprocal justice to trial participants in the post-trial period could be the provision of monetary rewards. The problem attached to such an approach is that it could promote undue inducement. It is usually agreed that monetary rewards should be of such a small amount in order for them not to form a reason for the participants to agree to enrol into the trial. However, given the vulnerability of the individuals within some developing countries and the health care settings, even small amounts of financial rewards may take on an undue inducement form. Furthermore once this behaviour of providing monetary rewards to trial participants becomes standard practice, the potential participants will start to expect financial reward for their services. Hence potential participants may accept to become enrolled into trials only with anticipation of pocketing money even if it was of little value to the researchers/sponsors.

Furthermore, adding a monetary reward to the trial participants means an increase in the total cost of the trial to the researchers/sponsors. This could hamper establishing interventions effective for illnesses that devastate these areas. If researchers/sponsors are attracted to developing countries due to the lower cost of the trial within these settings then by increasing the cost of running the trial within developing countries we may be causing researchers/sponsors to shy away from carrying out trials in developing countries. Instead researchers/sponsors may find it more cost effective to conduct their trials in places where no such demands exist.

Health benefits:

Health benefits to the trial participants may take different forms. The benefits may come about as a result of the provision of interventions through the trial or through the intensified health care services; follow up, medical care, and tests that these participants receive during their participation within the trial. Hence the participants may actually benefit from their participation in the trial through the improvement in their health status. Does this kind of benefit count as a fair division of the net gain at the end of trial between the parties? In order to answer this question we need to specify whether justice of reciprocity specifies that the benefits gained by the parties involved within the interaction have to come at the end of their interaction in order for justice to be served. However, this is not the case. The fair distribution of the benefits does not specify the time frame within which these benefits should occur nor does it specify that the duration of existence of these benefits and whether they could be permanent or temporary benefits. Furthermore, it does not call for an equal division of the profits between the researchers/sponsors and the trial participants, but rather a fair division of the benefits.

The answer to whether this benefit experienced by the participants during their participation within a trial counts as a fair share of the benefits lies within how health itself is viewed. We have argued in chapter three that health is considered as a basic human good without which people cannot live a thriving life. The improvements in the health of the trial participants whether it comes during their participation within a trial or at the end of it, does not change the fact that there has been an improvement in their primary need. An improvement in health may be a priceless goal to most humans especially those who are facing difficulties in

receiving basic health care needs. The importance of this benefit gains more value when compared to the benefits made by the researchers/sponsors which most commonly take the form of financial gains. Therefore, because of the value attached to health, the benefits gained by the participants could be classified as a form of post-trial benefits regardless of their timing. Hence, in principle justice of reciprocity is admirable and could be used to enhance the benefit of the trial participants, but to focus on it in the context of post-trial access alone ignores many other aspects of benefit aimed at enhancing participant outcomes. This point will be further discussed in the post-trial benefit section. Yet, several other issues which relate to post-trial access need to be discussed including the duration of access and the population which deserves to receive post-trial access.

Duration of access:

The provision of the proven intervention may be one of the methods of minimizing exploitation within the researcher-participant interaction. However; the provision itself gives rise to some concerns which in my view weaken the argument as it shows the failure of the concept in the prevention of exploitation of trial participants. Trial sponsor usually supply the proven intervention to the trial participants in the post-trial period anywhere from a couple of months to a couple of years, leaving us with the question: what happens after that time? Asking researchers/sponsors to continue supplying participants with the proven intervention as long as they need it seems superficially like a logical answer. However, this kind of support fails to happen in reality and is unfair for the researcher/sponsor. To begin with the researchers/sponsors fail to commit for this provision of the proven intervention for long

periods of time. To prove the failure of this approach, we will use a known case from Brazil which exemplifies the situation.

Pharmaceutical companies in Brazil found a loop hole within the healthcare system within the country (Petryna, 2009: 144-146). Although initially the pharmaceutical company supplied the participants with the proven intervention these sponsors approached research participants and informed them about their right to receive treatment from the state for their illnesses since health is viewed as a right and the country is obligated to provide the intervention to the population. The sponsors then told participants to sue the state with the aim of forcing the state into purchasing and providing an intervention for a specific population. Many participants won these law suits and the state was forced to purchase expensive interventions from the manufacturer who was earlier known as the sponsor of the trial. Where does this money come from? It is the health care system within the state that suffers immensely, particularly in the areas of preventive and primary health care. Money is pumped from government resources to purchase these expensive drugs (some of which may cost around \$2000 per patient per month) instead of supporting other development projects within the healthcare system. This form of post-trial access, usually affecting a small group of the population, appears unjust because it creates an unbalanced burden on other patients who either fail to receive health care services or suffer from delays in access to needed healthcare services although they are entitled to them (Saver, 2009). Therefore, we may conclude that in addition to the provision of proven interventions not falling under the duties of the researchers/sponsors which has been argued for earlier, forcing sponsors to supply the proven intervention to the trial participants makes the situation worse for the health care

system we are trying to improve. In addition this approach fails to prevent the exploitation of trial participants.

On the other hand, to demand that the researchers/sponsors supply the proven intervention to the trial participants at the end of the trial also places unfair demands on the researchers/sponsors. The researchers/sponsors are required to endure extra expenses in cases of successful or positive trials. They already put a lot of money into any given trial, even if with the intention of making much more money at the end. If developing countries inject too many demands of expenditures from sponsors, the sponsors in turn may decide it is not worth doing their research in developing countries. If They may stand a better chance of coming out ahead by carrying out their research in a developed country rather than developing countries even if it means carrying out trials for “me too” drugs or trials for minor conditions. If these demands are only made for trials being performed in developing countries and not industrialized ones, then the researchers/sponsors will shy away from trials which may in the end turn out to be much more costly than initially intended. The developing countries lose out in this case because the aim of performing the trials within developing countries is to find cures for illnesses that cause many unnecessary deaths within these populations. Furthermore, the sponsors will make every effort to shift the cost of providing the intervention to another authority, most likely the health care authority within the developing countries, even when they agree to supply the intervention and absorb the necessary production costs. This practice in return harms the developing countries rather than promote a net benefit.

Who should have access?

A couple of pathways could be considered when discussing who should have post-trial access. It could be argued that only trial participants should have access to the proven intervention. While a much broader view could be taken to argue that the whole population which suffers from the same illness must receive the proven intervention once the trial has ended. Each category will be discussed separately.

1. Participants of the trial:

Deciding whether participants in both arms of the trial should gain from the results once the trial has ended stems from the principle of fairness and the ideas of loss or abandonment. The latter two have already been discussed in detail in the earlier section hence only fairness will be discussed here.

The principle of fairness requires that we treat like cases alike and different cases differently. Each participant agrees to carry the burden of the trial without knowing which arm he or she will be assigned to at the time of enrolment. Therefore in principle, all trial participants should be viewed as similar cases and should receive equal benefits once the trial is over. At the same time, to hold that treating like cases alike through their provision with the proven intervention does not necessarily mean that outcome unfairness has been taken care of. For the interaction to be fair from an outcome perspective, the participants need to receive a fair share of the benefits generated from the trial. The fairness of this division of benefits does not translate only into the provision of the proven intervention. Other forms of benefit could

be provided to the participants and they would still lead us to conclude that there is fair division of the benefits. These will be presented while discussing post-trial benefits.

2. Whole population:

It could be argued that post-trial access should include those who were willing to participate in the trial but were excluded by the researchers/sponsors. This notion reverts again to the concept of fairness: treating like cases alike. However, people who have participated in a trial and those excluded from it cannot be defined as like cases. Those who actually participated in the trial and carried the burdens of the trial cannot be put in the same category as the nonparticipants or the general population. It has been discussed earlier that trial participants who had a contractual relationship with the researchers/sponsors have no entitlement to post-trial access. How can we then justify post-trial access to individuals who were never in a contractual relationship with the researchers/sponsors in the first place. They were not exposed to the risk of harm from the trial in order for them to claim that they have to have access to the proven intervention. The general population cannot be said to be like the trial participants and cannot be said to be deserving of post-trial access.

Furthermore, it has to be emphasized that the insistence on post-trial access whether to trial participants or whole populations reaffirms the misconception the public already may have about the roles of the researchers and those of the health care providers as has been discussed in more detail earlier.

3. Communities:

It could be argued that through their participation in the trial communities deserve to receive benefits at the end of the trial. The communities sometimes contribute to the trial through the use of its health care professionals or its equipment. Hence the community carried some of the burdens of the trial and therefore deserves a fair share of the benefits at the end of the trial (Gbadegesin and Wendler, 2006). Justice of reciprocity certainly agrees with this line of argumentation. Since the community has participated in the process, then it deserves to receive a fair share of the benefits at the end.

Considering the arguments presented earlier regarding post-trial access, it can be seen why this approach does not satisfy the requirements of fairness or justice. It is inconsistent, may be applied in only a limited number of trials, and is impractical. Furthermore, it emphasizes the confusion that surrounds the distinct roles of physicians and researchers. With this viewpoint in mind let us now present the arguments to support post-trial benefit and how it would help developing countries to a greater extent.

Post-trial benefits:

The fact that it is cheaper to perform trials in developing countries than in developed countries compels sponsors to move their trials to developing countries. In doing so the sponsors take advantage of the unfair circumstances that exist within these countries to advance their own interests. This does not mean that the interaction has to be unfair. We can ensure that trial participants and their communities are not exploited through the assurance that they receive a fair share of the benefits as a result of their participation in any

given trial. Since we have argued earlier that post-trial access does not satisfy the requirements for the assurance of fairness of reciprocity, we need to find other methods to ensure the fair benefit of trial participants and their communities.

There is no doubt that trial sponsors invest a lot of money into clinical trials with the aim of gaining benefit at the end of their venture. They claim that these trials are costly and risky (Trouiller et al., 2002). Yet, this goal of making a profit does not imply that only the sponsor should benefit from the trial. Other parties who have helped the sponsors in achieving their trial goals must also stand to gain. Sponsors should share their trial profits fairly with those who helped them reach their goal. Hence we need to be clear about what fair benefits mean.

Hawkins and Emanuel argue that fair benefit depends on three ethical conditions (Hawkins & Emanuel, 2008: 299). The conditions include: the research addressing a health problem specific or relevant to the developing country population, a fair selection of trial participants, and the trial having a favourable risk-benefit ratio. Two of these conditions will not be discussed here. The first one is the favourable risk-benefit ratio given that the assessment of harm has been presented earlier in chapter three and it was concluded that the potential trial participants and/or their communities should assess the acceptability of these harms. The second condition which will not be discussed here is the fair subject selection. Although this condition is very important, it relates more to the ethical appraisal of trial proposals. Therefore, this second condition relating to fair subject selection will be presented in more detail in chapter five when discussing the role of the RECs. The remaining condition presented by Hawkins and Emanuel will be presented here since it is relevant to this chapter, namely, the research addressing a health problem relevant to the developing country.

An example of research relevant to the health care needs of the populations is the study done by the institute of One World Health (iOWH). This institute is the first non-profitable research company wishing to develop new drugs and reuse old ones with global health needs in mind. The institute focuses on neglected diseases affecting poor people who cannot afford the expensive drugs. One success story realised by the institute's work occurred in 2004 during a trial conducted in India and funded by a \$10 million grant from the Bill and Melinda Gates Foundation. The iOWH in cooperation with the Special Program for Research and Training in Tropical Disease of the World Health Organization assessed the benefits of Paromomycin for treating leishmaniasis, a deadly parasitic disease spread by the bites of infected sand flies. The disease itself causes 60,000 deaths per year in Tropical and Subtropical countries. Paromomycin itself was ignored for a long time because it had become an off-patent drug. After the trial was over, the Indian government approved the use of the drug and furthermore, endorsed producing it locally. This example proves that research conducted in needed areas can provide positive outcomes, and also shows how the road to success can include both the researchers and the local community. Such collaboration further strengthens the acceptance of the trial results because they are tailored to community needs. This example shows how directly addressing the health care needs of the developing countries through carrying out research aimed at generating either information about the illnesses affecting these areas, or treatments for the condition helps reduce the 10/90 gap. Therefore, directly linking clinical trials to illnesses devastating the developing countries specifically will lead to improvements in the health care services and circumstances there. This necessarily involves training the local health care providers in the treatment of

the illnesses that affect developing countries' populations, establishing health care facilities in some cases (either mobile or stationary) (Crossette, 2001) where none exist, and following-up the participant populations medically or otherwise for extended periods of time. By following these steps the health of the populations in the affected countries will improve and unnecessary deaths will be prevented.

Having said that, we still need to specify the kind of benefit that would be expected in the post-trial period. We have presented earlier King's classification of benefits to the trial participants, however, given that direct benefit has been extensively discussed earlier in several areas, we will only discuss collateral and aspirational benefits here.

Collateral benefit:

This kind of benefit refers to the benefits that the trial participants experience through their participation in the trial even if they do not receive the tested intervention. Such benefits may include but are not exclusive to intensified medical examination and testing as well as receiving medical care which may not be available outside the scope of the trial. It could be argued that these kinds of benefits are in fact short lived and only last while the trial is being carried out. However, even if they are short-lived, they still have a major impact on the participants and may be defined as collateral benefit due to the way humans view health and value it. These intensified medical tests and follow ups may improve the quality of life of the participants as well as their health.

Based on the importance of health and how it is viewed Daniels argues that health becomes a special kind of good as a result of the unfair distribution of healthcare services and the

importance of health to individuals (Daniels, 1985). Therefore, someone's need for treatment for an illness e.g. tuberculosis, is the same regardless of whether the person resides in a developed country like the United Kingdom or in one of the developing countries. The improvement in the health of the individual participant is priceless and certainly worth more than any monetary compensation they may be offered. This kind of benefit should not be excluded when benefits to the participants are being considered.

Other means of increasing collateral benefit may include differential drug pricing and profit sharing. Without going into a lot of details regarding differential pricing, the application of this concept could solve many of the problems some developing countries are facing regarding the inability to provide certain treatments to their populations due to their expensive prices. The best examples are the pricing of the interventions used to prevent the transmission of HIV from mother to foetus. The failure of the provision of the agent to the population came about through the high prices attached to these agents. Despite the fact that the price was significantly reduced, the government was still unable to afford the agent and its price was still considered to be high. This meant that the local government remained unable to make the proven intervention available to the population in need.

Aspirational benefit:

Aspirational benefit refers to the benefits that are experienced by the community and future patients as a result of the study. Such benefits may include capacity building or training of health care professionals. This kind of benefit usually focuses on building local health capacities or purchasing equipment which may be considered as essential for the health care

system. Some developing countries lack so many essential factors for providing even the most basic health care services for their populations. There is usually a lack of health care facilities, shortage of essential medication and necessary medical equipment, and sometimes a lack of training of health care providers. Hence, in some cases, the researchers/sponsors may be required to purchase certain equipment, or to build health care facilities whether mobile or permanent in order to be able to perform their trial within developing countries. They may also need to train local health care providers and researchers on how to detect certain condition, test for them, and treat them. Usually at the end of the trial, these equipments and health care facilities are left for local use. This is a benefit that the community and future patients may benefit immensely from. Furthermore, the knowledge gained by the local health care providers and researchers will help in the better management of their patients and may generate more local research.

It is important to emphasize however, that despite the availability of different kinds of collateral and aspirational benefits, there is no shared international standard regarding fairness when it comes to collateral and aspirational benefits. (Pogge, 2002). Hence instead of anticipating the local needs by REC members within developed countries, local assessment of the anticipated post-trial benefits would be a more appropriate method to adopt since local community members are expected to have a better insight into local needs. This local assessment could be done through a negotiation process between the local representatives and the researchers/sponsors. Local representatives could include the REC members (with emphasis on the importance of lay members within the committee), the community leader, or the concerned potential participants. A negotiation step is extremely important between

the representatives of the local community and the researchers/sponsors. Several scenarios may be born through this negotiation process. One of these scenarios is that unreasonable or exaggerated demands are made by the local representatives. For example, the local community may demand the establishment of shopping malls or commercial residence buildings. In such cases, the negotiation process is extremely important. Both parties can discuss these terms and come to an agreement that is acceptable to both. On the other hand the researchers may offer the local community certain benefits which may be at a much lower level than what they could actually offer. In such a situation, the local community may accept these terms not because they represent the local needs but rather because of the existing local setup. Their analysis may be that some benefit to the community may be better than no benefit at all. In these situations, although benefit is being offered to the local community, the interaction itself may still be defined as a mutually advantageous consensual exploitative interaction. Hence these interactions should be prohibited based on the strategic intervention argument presented earlier in order to promote better alternatives. In cases where an agreement cannot be reached between the two parties, either of them may withdraw from the interaction.

All the conditions that apply to individuals making informed decisions regarding a trial should apply to the community as well. They have to receive enough information regarding the trial and their decisions have to be free from coercion or external pressure. The question that needs to be answered is who should actually make such decisions for the communities? There could be a range of options, including managers of health services, politicians, and civil servants. Although these options may be available within developing countries, I argue that

the most appropriate local representative to be charged with this responsibility is the local REC. The makeup of these RECs with representatives from the public as well as members with scientific/medical backgrounds makes us believe, at least from a logical perspective, that these boards would be capable of negotiating realistically with the research team. Being members of the community, both the medical and lay members of the community, the REC members would have an insight into the needs of the local community. Furthermore, this assessment of local needs by RECs' could incorporate the feedback of local health authorities or civil servants mentioned earlier. This is why it is extremely important to carefully select the lay members of the RECs to ensure that their level of education and knowledge about their local set up is acceptable. This point will further be discussed in more detail in the next chapter. The people involved in the decision making process may need further information regarding the kinds of benefits that have been experienced by other communities or populations. For this reason, Hawkins and Emanuel propose that a "publically accessible repository of all benefit agreements" (Hawkins and Emanuel, 2008: 303) should be established and be operated by an independent body such as the World Health Organization. Through this repository, benefits experienced by actual communities may be registered and they can be referred to by other communities in order for them to realize the kind and magnitude of benefits being discussed.

Another form of independent body supervision to ensure fair benefit is presented by Ballantyne in what she calls the global research tax (Ballantyne, 2005). Ballantyne's argument is based on two points. These include increasing benefits to the worse-off party in the trial and minimizing exploitation. Ballantyne begins by setting the boundaries that fall outside the

scope of what sponsors are required to do. The first point she stresses is that sponsors are not required to perform trials at a loss; secondly, they do not have an obligation of beneficence to populations in developing countries. Thirdly, sponsors need only share benefits that arise from the trial itself and not those previously acquired. The aim of this approach is to ensure that while sponsors still benefit from carrying out trials in developing countries, the gap between the benefits of the sponsors and those less well-off is reduced.

Ballantyne advocates imposing a global research tax which aims to maximize the benefits to the research populations and their communities while minimising benefits to the sponsor. She suggests that despite the implementation of a global research tax, trial sponsors would still benefit from their interactions with the participants and their communities. She justifies her calculation of benefit by comparing this approach with the next best alternative which is research being carried out within developed countries. Because sponsors can run trials faster and cheaper in developing countries it is more beneficial for them to conduct trials there. Statistics show that sponsors enjoy a 60% cost savings in clinical trial development by moving clinical trials from developed countries into developing countries (Ballantyne, 2005).

Ballantyne uses the Global Alliance figures for tuberculosis drug development to support her position. According to the Global Alliance, the cost of phase III trials in the United States is 22.6 million dollars whereas the cost of carrying out the same trial in Uganda is 8.2 million only (Global Alliance, 2001). These numbers mean that a net profit gain is anticipated for sponsors even when global research tax is set as high as 90%. This means that instead of sponsors performing trials on trivial drugs or repetition of similar trials, a more serious focus on intervention relevant to the developing countries' populations will have to be established.

Applying the global research tax would mean a reduction in the pharmaceutical companies' ability to perform marginal trials in some areas. The advantage to this step comes in two fold. The first is the reduction in the focus on what is known as "me too drugs" and then a shift to research in areas where cures are truly needed. Secondly, the tax paid will aid the communities in the developing countries to develop their health care services among other areas where improvements are needed. However, Ballantyne stresses that deciding on the most appropriate level of global research tax for all parties concerned warrants further examination. To be effective, this tax will have to be applied to all for-profit sponsors of trials because for-profit organizations are not expected to voluntarily give up part of their profit, especially when realising inconsistent profits and need for enhanced profit compared to that gained from the next best alternative. The calculation of the tax should exclude the costs of the trial to the sponsors and tie directly to the cost of conducting the trial in developed countries. But, why should sponsors feel obligated to share their profits in developing countries when they are not required to do so in developed countries? The answer to this question lies in the unfair circumstances that already exist in developing countries. Hence, there is a need to maximise the benefits to those worse off in the interaction.

"the notion of fairness to persons as such- according to which treating persons as such requires redressing , within limits, those morally arbitrary disadvantages that significantly impede their flourishing"
(Buchanan, 1990: 234).

The main idea behind the global research tax is that it has to maximise the benefits to those worse-off in the interaction. Ballantyne's approach although creating additional expense for the sponsors, still allows for an expected margin of profit compared to gains from trials performed in developed countries. From another perspective imposing a global research tax would broaden benefit to the community by fulfilling other basic needs outside of health care services. Some developing countries lack proper sanitation, clean water supplies, safe food sources etc. Therefore the benefit to the community could happen through improving access to these basic goods rather than focusing on health alone.

The weaknesses with Ballantyne's global research tax approach come at several levels. On the sponsors' level, it could easily be seen how trial sponsors could redirect their trials to other locations where no such demands for taxation are made. If sponsors can still perform their trials in other areas where they are allowed to keep all of their profit, then surely this is what they will do. Hence as a precautionary step to prevent this selection of locations, trial sponsors should be asked to truly consider the cost of performing trials in developing countries. When this is done, and it becomes clear that the sponsors would still be at a profit even after the global research tax is deducted then perhaps sponsors will be encouraged to perform more trials within developing countries. Furthermore, to try and reduce such a resistance from pharmaceutical companies against performing trials in developing countries, persuasions benefits could be provided to trial sponsors in order for them to agree to perform trials within developing countries and pay the global research tax. One example of such persuasive benefits may take the form of extensions on patency rights which translate to extended benefit. Furthermore, the application of a global research tax would exclude the

hesitation the researchers may have in choosing the locations where their trials will be carried out. It would be better for the sponsors to perform their trials within developing countries focusing on health care issues relevant to that population, and at the same time reduce the cost and increase their profit. Hence a shift is created where only relevant trials to developing countries' populations are performed which at the same time benefit the sponsors of the trials.

On the other hand, Ballantyne assumes that the benefit provided to the authorities within the developing countries would be directed to the good of the general populations. This is not entirely true; some governments may use the extra income for the purchase of weapons or for the support of certain groups within the society. Hence, although the intention is to maximize the benefit to the worse off, this may still not take place in reality. In order to solve this issue, an independent not-for profit agency could be assigned with the responsibility of allocating these funds for example the World Health Organization. This would ensure that the goals of the global research tax are taking place rather than going in different directions especially in the cases of corrupt governments.

With these extra conditions, fair benefit ensures that (Hawking & Emanuel, 2008: 303):

1. The participants are selected for scientific reasons;
2. Trial poses few net-risks
3. There are sufficient and long lasting benefits to the population and their community
4. The population determines the level and kind of benefit to be provided by the researchers

5. The repository offers the population a chance to compare and assess the benefits being offered to them.

Fair benefit also makes sure that all the benefits that the community may enjoy are considered and taken into consideration and that decisions regarding this matter are made by the population or community concerned.

Post-trial benefits take on a wider perspective of the form of benefit that the trial participants or their communities may enjoy after the trial has ended when compared to post-trial access. There are several reasons for demanding post-trial benefits in the communities hosting the clinical trials. First of all, the community accommodating the trial endures some costs and needs to gain in return for its interaction with the sponsors. Most importantly, post-trial benefit takes on a wider perspective of the benefits the trial participants should receive as well as their communities may enjoy as a result of their participation within the trial. In addition to considering direct benefits, it also includes collateral and aspirational benefits. Fair distribution of benefits between the sponsors and the communities represents my second argument for supporting post-trial benefit.

Conclusion:

The chapter has focused on post-trial benefits to trial participants and their communities from two different perspectives; a post-trial access and post-trial benefit. The post-trial benefit approach broadens the spectrum of acceptable benefits to trial participants by considering several other forms of benefit including direct, collateral, and aspirational benefits. Furthermore the chapter introduced a global research tax concept with the aim of

increasing the benefits to the trial participants and their communities which should be monitored by an independent authority.

To ensure exploitation is minimized and outcome fairness achieved once the trial is terminated, participants and their communities have to receive a fair share of the net benefits gained from the trial. Sponsors have no obligation to provide the proven intervention to the trial participants because they do not fulfil the physician role normally required to act in the best interest of the patient. However, this does not mean that the sponsors have no duty whatsoever towards the trial participants. They must still respect the trial participants and minimize harm to them.

Post-trial access has been shown to be impractical and to view benefits to participants from a very narrow perspective. We have shown that this approach is problematic for several reasons. Even when there is a will to provide proven interventions to participants, the sponsors are unable to do so directly because of local authorities' regulations and requirements regarding drug approval and marketing. Also, the introduction of the proven intervention within the country where the trial has taken place does not rest in the hands of the sponsors themselves.

On the other hand, post-trial benefit takes on a much broader perspective of benefit and looks at it from a fair benefits point of view. If we view health as a basic good for humans without which people are unable to flourish, we can then argue that since trials aim at issues related to health, then it is these potential participants and their communities that have to decide on the kind of benefit that should be provided to them. Both the populations and their communities carry some of the burdens of the trial, the participants by accepting the

risks of the trial and their communities through the use of resources and health care providers. Admittedly there are different kinds of benefits available as options to both the participants and their communities. We have divided the benefits into direct, collateral, and aspirational. We have argued that in order for the benefits gained by the participants and their communities to be defined as fair, the participants have to be selected based on scientific reasons and not convenience to the sponsors or vulnerability of the potential participants; there have to be sufficient and long lasting benefits to the population and their community. They must be given the opportunity to negotiate the level and kind of benefit to be provided by the researchers/sponsors. The repository offers the population a chance to compare and assess the benefits being offered to them. This negotiation process ensures that both parties come to an agreement prior to the initiation of the trial regarding the anticipated post-trial benefits to the community. At this stage if any unreasonable or excessive demands are placed on the research/sponsors or alternatively if the benefits offered by the researchers/sponsors are not acceptable to the local community, both or either party may decide to withdraw from the interaction.

Furthermore, we have discussed Ballantyne's global research tax as a method of increasing aspirational benefit. This approach requires the collection of a global research tax from all for-profit sponsors. This tax should then be placed under the supervision of an authority, the United Nations or the World Health Organization for example, in order to ensure that this money is spent on the improvement of health care within developing countries.

In order to maximize the benefits to the trials to developing countries populations, a post-trial benefit approach needs to be adopted instead of the narrow post-trial access approach.

Chapter Five: RECs and the Prevention of Exploitation

Introduction:

Discussions in earlier chapters led us to conclude that exploitative interactions need to be prohibited, even mutually advantageous consensual ones. This should be done in order for non-exploitative interaction to be promoted. Furthermore we need to ensure that social value is present especially when trials are intended to be carried out in developing countries. What has not been presented so far is who should take on this responsibility. This chapter will focus on that issue by discussing RECs. A comprehensive analysis will be presented regarding REC's roles and responsibilities as well as their formation. The chapter will argue that local RECs should be given the responsibility of assessing trial proposals. This is not due to the lack of experience of RECs within developed countries nor is it an attempt to abolish the discrepancies between the decisions of different RECs. I think these discrepancies will continue to exist considering that RECs are urged to focus on social value despite the fact that they may all, in the end, receive the same training required to become members of RECs. The reason for calling for local review rather stems from the lack of insight of distant RECs regarding the local needs within developing countries. Local RECs have the knowledge regarding social value and acceptable benefits to the local society. This being said, it has to also be emphasized that certain changes to the local RECs need to be implemented. They

need to receive more training regarding ethical appraisal of trial proposals and their makeup needs to be changed to constitute a majority of lay members.

Admittedly RECs are among the first groups of people to review research proposals prior to their initiation. Other groups may include the researchers and the sponsors of the research. However RECs have the responsibility of ethically assessing trial proposals.

From a historical perspective, establishing independent RECs provided a necessary measure for ensuring research participants' authority in deciding whether to participate in any given trial. The aim was to protect those potential participants from unnecessary harm and or abuse. The need for stricter controls arose not only in response to the few trials corrupted by mistreatment of trial participants or their lack of consent that became publicly known but also through whistle blowers. Perhaps the two most commonly known to have caused dramatic changes in research ethics after the Nuremberg are the publications of Beecher and Pappworth who have accumulated and published information about unethical research done in the post Nuremberg era (Harkness et al., 2001). Beecher for example presented information relating to twenty two studies as evidence of unethical behaviour. To him this form of behaviour did not form the exception but rather widespread practice amongst researchers. Through these publications, the public, RECs, and regulators of research involving human participants saw the failure of the existing review process and that it was not performing as well as we thought it was in the prevention of exploitation of trial participants.

There are many different settings within which RECs exist. Not-for-profit RECs reside within academic institutions, universities, or governmental agencies. Generally these RECs are

viewed as less problematic than their profit-driven counterparts because it is claimed that they run independently from the institution and the members volunteer to perform their responsibilities as members of the review board. On the other hand there are for-profit RECs. The majority of review processes taking place today especially in the United States are carried out by RECs set up and funded by pharmaceutical companies (Bekelman et al., 2003). Although these RECs generally hold the same structure as not-for-profit REC's, their attachment to for-profit organizations brings their independence under the spotlight. Pharmaceutical companies often hire a contract research organization (CRO) to conduct a trial. The CRO usually takes care of the clinical trial from every aspect including participant recruitment and ethics review. This is evident from the fact that in 1994, 63% of the clinical trials were carried out within academic institutions compared to only 26% nowadays (Lemmens and Elliot, 2006). For the purposes of the discussions within this chapter however, this distinction between for-profit and not-for-profit committees will not be further perused. Rather the discussion here will focus on the issue of which REC should review trial proposals intended to be carried out in developing countries, an REC within the sponsoring country or the one within the developing country itself.

Most well established, well recognised and organised RECs reside in developed countries. These RECs have made substantial headway towards establishing standards for research involving human subjects. REC members have the ability, through their experience in reviewing trial proposals, to prevent harm and exploitation of trial participants. Trial proposals have to be submitted to an independent REC and its approval has to be sought prior to the initiation of the trial and recruitment of trial participants into the trial. Obtaining

this approval has become one of the essential steps in getting a trial started. In fact, some countries have made this approval process a legal requirement for trial initiation (Varmus et al., 2003). In the United Kingdom, the United Kingdom Ethics Committee Authority (UKECA) is responsible for establishing, recognising, and monitoring the ethics committee within the country (Alberti, 2000; Tully, 2000). The UKECA requested the National Research Ethics Service (NRES) to establish a central advisory committee. The main role of this central advisory committee is to aid RECs in delivering consistent and fair decisions as well as providing guidance and training to REC members (National Research Ethics Advisors' panel). In the United States, Federal law requires that researchers obtain REC approval before conducting a trial. However, this only applies to federally funded and regulated trials. Privately funded trials do usually solicit some type of review and approval however it is not legally required. In addition, United States regulations permit the transfer of oversight responsibilities between RECs meaning that a multicentre trial may maintain a centralized review (CFR, 2010).

The International Council on Harmonization defines the independent review boards or RECs as a "group formally designated to protect the rights, safety, and well-being of humans involved in a clinical trial, by reviewing all aspects of the trial, and approving its start-up" (ICH, 1996: P4). These boards emerged at different time points within different countries. For example, in the United States RECs were first established in 1970 (Law & Society association, 2007) whereas in the United Kingdom they gained official status only in 1991 (Williamson et al., 2000). Since their establishment, RECs have been interpreted to perform different perhaps sometimes contesting roles. On the one hand RECs are required to ensure the

welfare of the trial participants through the assurance of adequacy of enrolment of human participants within the trials, their protection, and their safety. This step also assures the potential participants that someone other than the research team has reviewed the trial and found it acceptable for humans to be enrolled into the trial. The aim is to protect potential participants from unnecessary harm and/or exploitation. On the other hand, RECs are also required to ensure that potential participants exercise freedom of choice. This is done through the assurance of existence and exercise of informed consent and warrant research participants' authority in deciding whether to participate in any given trial. These roles will be discussed in further detail later on.

Informed consent will not be further discussed here given that it has already been discussed in chapter two. This chapter will focus on RECs, their roles and formations. Furthermore, the issue of discrepancies between different REC decisions will be discussed, how and if it can be prevented, and how exploitation fits into the role of the RECs.

The role of review boards:

Since their inception, REC responsibilities have expanded to include the protection of potential participants from unacceptable risks by ensuring participants understand the consequences of their participation, and maintain decision whether to participate (CIOMS, 1993). To this end, the REC's role in protecting potential participants in advance and through periodic monitoring is highly emphasized (Moodley and Myer, 2007).

Many experts have proposed criteria for RECs for assessing research proposals. Emanuel and colleagues proposed seven essential requirements that define a general framework to use

when evaluating the ethics of clinical and epidemiological research (Emanuel et al., 2000). These criteria include: social and scientific value, scientific validity, fair subject selection, favourable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects. The suggestion of these guidelines came with the aim of providing clear guidance to different REC members located within varying geographical locations to assess trial proposals in the same way. Some have gone as far as requiring that a uniform standard should be followed in the review process, with exception given to local perspectives regardless of the trial location. Voo and colleagues state:

"While procedure mechanisms should be allowed to differ between and within countries, ethical standards that pertain to universal human rights and welfare should be consistent."(Voo et al., 2008: 108)

Similarly, some countries such as Malaysia and South Africa have implemented the Good Clinical Practice (GCP) guidelines (DOH, 2000). The GCP first published in 1995, is a set of World Health Organization guidelines for steering the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials (WHO, 1995). These guidelines have become the industry standard and adherence to them assures accurate and credible reporting of results, as well as protection of the rights, integrity, and confidentiality of trial participants (Petryna, 2009). This approach as well as the formation of the NRES in the United Kingdom is an attempt to bring different RECs under one set of guidelines or standards (Edwards et al., 2004). However, even with the implementation of similar guidelines across borders by different RECs, the decisions reached by these different RECs

may still differ significantly. To see how this may be the case, a presentation of how RECs may prevent exploitation will be presented.

Given that the main roles of RECs is seen as the assurance that trial participants are enrolled into the trial only with their consent (Garrard and Dawson, 2005) and the protection of potential trial participants from harm, we need to establish first how these roles are linked to exploitation.

RECs and procedural unfairness:

From a procedural perspective of unfairness, RECs are required to ensure that trial participants are given the freedom to make a choice regarding their enrolment into a trial and that they receive enough information that will aid them in their decision making process. This is indeed one of the areas where RECs are sometimes accused of focusing their attention on. This accusation holds that REC members address the wording and content of informed consent forms and information sheets without properly scrutinizing other ethical issues associated with the research proposal such as risks to the participants (Macpherson, 1999; Kass et al., 2003), or participant selection criteria. Although RECs must very carefully assess the kind and amount of information released to potential participants, this should not be the only issue drawing attention from REC members. If it did, then the existence of RECs is not all that important as “a special research information officer” trained at scrutinizing such requirements could replace the whole REC (Garrard and Dawson, 2005: 420). Therefore the assurance of procedural fairness is one of the methods through which RECs may ensure that potential trial participants are not exploited through their enrolment into any given trial.

RECs and outcome unfairness:

The second perspective of unfairness comes through the focus on the outcome of the interaction. In order to prevent unfairness and hence exploitation of potential trial participants, RECs need to assess whether the potential trial participants and their communities will receive a fair share of the benefits anticipated from the trial. This protection from unfairness is achieved through the assessment of the requirements put into place for the evaluation of the ethical appraisal of clinical trials (Weijer and Anderson, 2001; Lansang and Crawley, 2000). Emanuel and colleagues proposed seven essential requirements that define a general framework to use when evaluating the ethics of clinical and epidemiological research (Emanuel et al., 2000). These criteria are summarized in the following points:

1. Social and scientific value
2. Scientific validity
3. Fair subject selection
4. Favourable risk-benefit ration
5. Independent review
6. Informed consent
7. Respect for potential and enrolled subjects

Clearly these criteria offer guidance to researchers on all matters of ethics when conducting studies involving human participants. However, certain alterations to these requirements are in order. Hence each one of these criteria will be presented and discussed separately. Furthermore, certain additional points need to be considered which directly affect the ability

of RECs to assess unfairness. These include conflict of interest and proof of registration. Each of the criteria presented by Emanuel et al. will be discussed separately with justifications given to each alteration made to the original criteria proposed. However, both the assessment of harm and informed consent will not be presented here since they have already been discussed in detail in the chapter two.

Social value:

Although Emanuel et al. combined social and scientific value in one requirement; only social value will be discussed here. Scientific value will be combined with scientific validity and will be discussed as one requirement separately.

Although social value has already been presented through the assessment of harm in chapter two, a more detailed analysis will be provided here. To ensure that social value receives proper consideration during the review of a given proposal, RECs must first determine who will most likely benefit from the trial results and thereby determine whether certain populations need to be enrolled into the trial. Emanuel et al. describe four conditions that benchmark social value in a trial (Emanuel et al., 2004). First of all, it has to be determined who will benefit from the trial results: the community from which participants are recruited, the host country population, or a different population altogether? As discussed earlier, the direction of the benefits of the trial to other populations is not problematic in and of itself within research given that any research result may benefit populations either geographically distant from the participating population or may benefit future populations. However given the circumstances within developing countries; social value has to be ensured

in order for sponsors not to take advantage of the vulnerabilities of the potential participants and the lack of health care services within these settings. In cases where the benefit is anticipated to be directed at the potential participants or their communities, the level and kind of benefit needs to be assessed to ensure that the potential participants receive a fair level of the anticipated benefits. Secondly, the potential trial value to prospective beneficiaries should be established. Each population or community ranks health care priorities differently and this in turn depends on the local setting. For example, a community suffering from a treatment resistant strain of tuberculosis may put discovery of therapeutics designed to fight this illness as their top priority. Another community may not rank this research goal with the same urgency. Thirdly, trial results should reach members of the community in order to maximize social value. The results should not be hidden away in journals and health care provider recordings. This action gains momentum when the trial itself becomes part of a health care development plan within the concerned community. Fourthly, the REC needs to also assess whether the conduct of the trial would undermine the existing health care system within the community. In some cases, even socially valuable research which has the potential of compromising the already compromised health care system may not be justified or approved by the REC.

On the other hand, in trials where all the benefits are expected to be directed at different more well off, perhaps distant, populations, the REC needs to question why the researchers/sponsors want to carry out their trial at this given location or to recruit this specific population.

Furthermore, REC members need to assess the aspirational and collateral benefits which may be generated from the trial and not only the direct benefits to the trial participants. They have to ask about equipment, health care facilities, and training of local health care providers during the trial and whether these will continue to exist after the trials. Also REC members need to ensure whether other forms of social benefits may be provided by the researchers/sponsors outside the scope of health care services.

Scientific validity and value:

The assurance of scientific validity of trials is an essential requirement for an ethical trial. I will address this specific point from two different but interlinked perspectives. The first one focuses on the issue of scientific validity and value and the other one focuses on the concept of equipoise.

There are many reasons why scientifically invalid or valueless trials should not be permitted. Some of these reasons include the diversion of limited resources to trials which will not generate any new information and at the same time expose trial participants to harm without the existence of potential benefit to future populations. However despite this being an important step in the review process, the REC does not seem to be the right authority to perform the task. Scientific validity links to the REC's mandate. However, scientific validity and ethical review seek to answer a different set of questions. Scientific review and the assurance of scientific validity and value assess the scientific quality of the trial, the ability of the research to generate new knowledge, the appropriateness of the methodology used in the trial, sample size, use of randomization, population stratification, sources of bias and the

ability of the trial to achieve its objective (Black, 2001; Emanuel et al., 2000; Schlesselman, 1982). Scientific review committees therefore, typically consist of clinical scientists, medical doctors, safety managers, regulatory affairs professionals, and statisticians (Federman et al., 2002). This combination of specialties makes it easier for the scientific review teams to properly consider and analyse the trial proposals from a purely scientific perspective. Separating the review process in this way ensures that only scientifically valid research receives ethical appraisal. Some trial proposals appear ethically sound on the surface, but may in fact be scientifically invalid or valueless. For example the research may fail to generate new knowledge or may simply repeat conduct of a previous trial. The Office of Protections from Research Risks (OPRR) states that:

“A proposal without scientific merit can on the surface appear to be ethically acceptable, but the fact that it will not produce new or usable data does not justify the use of human participants regardless of the level of risk.” (OPRR, 1993)

Scientifically poor or invalid research gives no benefit to the community and therefore should be limited, as should trials investigating previously answered questions because such practice may deny participants proven interventions, or place them at risk without anticipated benefit to them or to future populations, or both (Savulescu et al., 1996). Scientifically bad or poor science may result in the wasting of resources, exploitation of participants, publication of misleading or false information leading to the promotion and introduction of ineffective treatments as standards of medical care, or the overlooking of effective ones (Savulescu et

al., 1996). Carrying out any form of research which lacks scientific value may indirectly harm future populations. For example, the publication of misleading information may lead researchers to shy away from performing future research in the same field, and may also establish wrongful conclusions concerning the research area. This shift in future research priority can indirectly harm the community as well as future patients. Valueless research also wastes scarce resources that ultimately should be reserved for beneficial trials (Coughlin and Beauchamp, 1992). Enrolling participants into valueless research exposes them to harm without foreseen benefits.

Some argue, as Hunter does, that the scientific analysis of a trial proposal should not be the responsibility of the REC members as is the case for the NHS ethics committees (Hunter, 2007). Hunter supports his position by emphasising that most of the REC members do not have the expertise to carry out scientific review. Also, performing this role puts an extra burden on REC members. Scientific validity review entails understanding and rationalising highly technical details, which the REC members may lack capacity to do properly. I agree that scientific review should be delegated to another committee specifically concerned with the assessment of the scientific value and validity of the trial proposal. However, in order for this approach to be effective direct communication should be established between the scientific review committee and the REC. The scientific committee has to provide the REC with detailed reports regarding its scientific review, and the report has to be presented in a language comprehensible to the non-medically and non-scientifically oriented REC members. Some of the information that should be communicated may include the strength of the scientific design and methodology, the practical feasibility of the research design, the

probability of the trial meeting its goals, and the qualifications of the investigator to carry out the protocol (Federman et al., 2002).

The anticipated results of such an arrangement are that RECs review only scientifically valid and valuable trials and at the same time avoid potential conduct of scientifically praiseworthy trials in unethical ways. Hence REC members use their time more efficiently and make more sound judgements. In the United Kingdom, this approach is used where NHS RECs are discouraged from assessing scientific validity of trial proposals. This structure ensures that another perhaps more qualified committee takes on the responsibility of assessing scientific validity and value.

Another important aspect of the scientific validity review links to equipoise. It is crucial for any initial assessment of a clinical trial to study equipoise in relation to that specific trial proposal. In the traditional sense, equipoise literally means a genuine uncertainty existing within the medical community as to which therapeutic option is best for the patients. This uncertainty could reside with the individual clinician as suggested by Fried (Fried, 1974).

Individual or theoretical equipoise refers to individual physician or health care provider and is considered by some as justified reason for a physician to request to perform a given trial. However, a physician rarely finds himself or herself in this situation because he or she usually has a preference for one intervention over another. The second kind of equipoise is known as medical or collective equipoise (Kuhse and Singer, 2006).

This kind of equipoise refers to scenarios where the whole medical profession or a group of health care providers have a genuine uncertainty about which method of treatment is superior or better than the other. Clear and honest uncertainty as to which intervention

provides the most benefit to future patients' well-being must be present before recommending clinical trials to help resolve uncertainty. Equipoise then plays a role in the initiation as well as continuation of trials evaluating the health outcomes of participants within the trial. This is what Kukla calls the traditional principle of equipoise:

"In order to begin or to continue an experiment on human subjects, one must be in a state of equipoise with respect to the relative expected health outcomes for participants in different trial arms."

(Kukla, 2007: 171).

Many arguments surrounding equipoise have unfortunately assumed that equipoise finds roots within the physicians' duties towards their patients. For example Miller and Weijer both see equipoise as a conflict between the responsibility of a physician to benefit his or her patients, and the role and responsibilities of the researcher. These scholars state:

"Equipoise has been presented as a way of resolving the moral tension between the physician's commitments to the personal care of her patients on the one hand, and her commitment to a program of research on the other." (Miller and Weijer, 2003: 93).

Similar to Kukla's views, Miller and Brody (Miller and Brody, 2002) claim that physicians and researchers have distinct roles. They see researchers as removed from therapeutic duty towards their trial participants and therefore insist that equipoise should not pose an ethical constraint on research. Chiong arrived at this same conclusion but through a different route of analysis (Chiong, 2006). He argues that because physicians never actually assume

“uncompromised patient-centred” therapeutic duty presumed to be in place, and in fact may make trade-offs that compromise their patient’s care, equipoise should not play a role in constraining research.

However, both arguments initiate from confusion between the physician-patient relationship and the researcher-participant relationship. Equipoise is supposed to resolve conflict between the two. It requires investigators to act in the best interest of future patients, i.e. finding out which intervention proves better than the available alternatives. By doing so, and resolving any uncertainty, researchers actually help physicians to provide better care for their patients. Therefore, regardless of whether the researcher is a clinician or not, the aim of his or her research should focus on resolving existing equipoise for the purpose of advancing patient care. In an attempt to resolve the issues concerned with what she calls “traditional equipoise” Kukla offers a new approach to equipoise which she calls PE*:

“PE*: In order to begin or to continue human subjects research, one must be in a state of equipoise with respect to whether or the extent to which the intervention being tested *should* be made accessible to the population that falls under the scope of the research.” (Kukla, 2007: 180)

Therefore, equipoise exists within clinical trials only when there is genuine uncertainty among the researchers as to whether the intended research would better serve the population it is recruiting, and furthermore this criterion is not limited to the participants within the different arms of the trial, or to clinical effectiveness. This very precise perspective

of equipoise takes into account the people concerned, which is an important consideration when dealing with any type of vulnerable population. This philosophy imposes upon investigators and reviewers the responsibility of investigating the most appropriate way of addressing the health needs of concerned populations within hosting developing countries. Admittedly, exceptions occur when using equipoise as a guiding principle in trial design and approval. For example, Kukla mentions two exceptions to the traditional view of equipoise, i.e. carrying out the trial in a population other than the one expected to benefit from the results, or implementing research with the goal of generating new information about an intervention rather than comparing existing ones. The newly generated information may influence further research, but may not benefit the community directly.

The first of Kukla's exceptions refers to carrying out a trial in a community when at the outset there is knowledge that results will benefit a totally different community or population rather than the local one. Kukla argues that her definition of equipoise may hold greater stance when the trial results can be generalised from the place of trial conduct to the other populations. However, equipoise fails when the trial results do not apply directly to the population intended to benefit from the study. The opposite situation where one can generalise trial results from the study group to the one intending to benefit from the trial means that the population participating in the trial falls under Kukla's definition of equipoise. However, satisfying equipoise in this case does not automatically imply an ethical trial. Kukla emphasises this point:

“Satisfying PE* should not be researchers' only ethical concern.”

(Kukla, 2007: 193)

The second exception to equipoise where the research aims to generate new knowledge, does not present a breach of ethics as long as the research refrains from violating all other ethical requirements e.g. lacking informed consent. Kukla therefore, suggests that equipoise on its own does not dictate whether a trial is ethical, but rather represents one of the criteria considered when reviewing a proposal. Kukla's first argument relating equipoise to generalisation of results between populations however ignores an important point. All forms of research including clinical trials have the common goal of generating new generalizable knowledge. Selecting potential participants therefore relies heavily on factors other than generalisation such as ease of access to the population, and perhaps lack of regulations. Trial focus should therefore consider equipoise concerning involved populations. Equipoise also links to the concept of social values however social value has already been discussed in detail above.

Hence scientific validity and value review of the trial proposal should assess not only the pure scientific aspect of the trial but should further allow for the analysis of the existence of equipoise as well and should be done by the scientific review committee. Hence the scientific review report should include details about equipoise as well in order for the REC members to assess the proposal as a whole.

Fair subject selection:

The REC has to scrutinize and determine the reasons underlying the selection of the trial participants. This precautionary measure ensures that trial participants get selected based on scientific justification rather than reasons of convenience tied to lack of regulations, less

stringent ethical review, or lower risks of litigation (Moodley and Myer, 2007). So, trials recruit participants with the aim of improving health care services, or finding a better medical intervention. A problem frequently encountered in trial conduct is the recruitment of participants for reasons other than scientific advancement and social value, such as cost lowering for sponsors, lack of regulations, taking advantage of participants' vulnerabilities etc. RECs need to ensure that the objective of the trial justifies performing the trial within the chosen community. Several factors sometimes compel researchers to carry out trials within developing countries for example the prevalence of the illness within that region alone or the need to find less expensive but effective treatments for conditions affecting these populations. Individuals should not enter into a trial simply to appease sponsor anxieties in obtaining the required number of participants, or when lack of regulations undermines the safety of the participants. This point is certainly stressed in some international guidelines where vulnerable populations may only be recruited once an anticipated trial benefit to participants has been firmly established, or when trial execution depends on enrolment of these vulnerable research subjects.

Independent review:

Although this point is certainly a crucial point in the assurance that the clinical trial is ethical and has received ethical appraisal from a party other than the research team, for the purposes of this chapter it does not provide much guidance since we are using the guidelines to identify aspects which should be scrutinized by REC members during their review of trial proposals. Hence this requirement will not be discussed any further.

Respect to potential and enrolled participants:

When it comes to respect, RECs have to be very careful regarding the meaning of respect which they have to focus on. There are many different accounts of respect (Feinberg 1975; Hudson 1980). One of the simplest is the distinction that has to be made between respect as behaviour and respect as an attitude. In the first, the respect for something or someone stems from the avoidance of breaching limits or boundaries, for example a driver not exceeding the speed limit on the road. On the other hand, respect as an attitude refers to the expression of our feelings towards the respected object, for example respecting a person. RECs need to focus on the second kind of respect which requires some preconditions. Respect is most broadly defined as the respect owed to all people regardless of any other factors e.g. characteristics or social status. Some writers have argued that certain conditions must exist in order for respect to be fulfilled. To begin with, the respecer must be a person; secondly, the respected person has to be seen as valuable independent of the respecer's desires or goals, and thirdly, the respect cannot be devoid of reason, the person we respect has to have certain characteristic which make us respect that person (Cranor, 1975). Yet there are arguments that state that respect is not an option but an obligation, it has to be done (Wood, 1999). Perhaps the most influential discussions about respect have mainly revolved around the Kantian perspective on this issue. His main argument concerning respect is that persons are owed respect because they are rational beings (Kant, 1785/1996).

The respect owed to those rational individuals, according to Kant, is unsurpassed and unconditional because they have an intrinsic worth or dignity. It is because of this dignity that they are not to be used as mere object. Since this point has been discussed at length in

earlier chapters, it will not be presented again here. The unconditional requirement for respect is built on two main features, that of their ability to determine ends and their ability to act autonomously (Wood, 1999; Korsgaard, 1996; Hill, 1997). The ability to set ends is based on the person's capability to use rationality and reasoning to make a decision. On the other hand the ability to act as autonomous individuals relates to their ability to make choices freely that will fit in with their future plans and therefore life.

Through Kant's writings, many writers have stressed the importance of respect for autonomy and this respect can be divided into negative or positive respect. From the negative perspective, respecting a person comes in the form of not interfering with their decision making process by not coercing them or manipulating them for example. On the other hand, positively respecting a person's autonomy comes from encouraging the individual to make his own choices and allowing him to control his life.

Potential participants garner respect by having a stance in providing social benefit from the results of the trial. Also, researchers should respect participant confidentiality and inform them of any adverse events that may unexpectedly occur during the clinical trial. Participants should also feel free to withdraw from the trial if needed, and should not be forced or coerced to continue their participation in the clinical trial. All these points have been discussed in detail in chapter two; the emphasis here is on the REC members ensuring that due respect owed to the trial participants is ensured.

Conflict of interest:

Conflict of interest is the suspension of primary interests for the sake of secondary interests (Thompson, 1993). Conflict of interest can be viewed from two perspectives: the conflict of interest of the REC itself through its members and the conflict of interest of the researcher and their team. From the perspective of the REC, the conflict may involve the whole REC or the conflict may exist through an individual member of the REC.

When it comes to conflict of interest of whole RECs two issues need to be considered, those relating to the overriding power held by the sponsoring country or agency and the other relates to the conflict of interest of the REC in relation to its affiliation with an institution.

The overriding power held by sponsoring countries when conducting trials in developing countries raises a concern from two perspectives. First of all, Sponsoring wealthy nations or companies sometimes donate large amounts of money to either the governments of the developing countries or the local institutions where the REC performs its functions. This money helps support a developing country on several fronts or may help an institution on so many levels. A local REC may show reluctance in refusing a research proposal from such a developed country. This reluctance may stem from the fear that the refusal of a research proposal will lead to cessation of aid in other aspects or levels. Furthermore, some RECs within the United States charge pharmaceutical companies for the review of their protocols (Emanuel et al. 2006). In gaining financial reward RECs' decisions may become clouded by financial support and access to new drugs as well as prestige obtained when their institution conducts a study. RECs in the United Kingdom do not charge for their services thus removing at least a financial aspect from the conflict of interest framework. In addition, researchers

from the sponsoring country retain the upper hand when deciding how the research will be conducted and how the funds will be allocated (Whittington, 2004).

The second kind of conflict of interest which relates to the affiliation of the REC to an institution relates more to the conflict of interest between advancing the interests of the institution and their capability to advance their primary responsibilities. Some critics, such as Emanuel, suggest that although RECs cry independence, they are not totally independent. An attachment to the same institution from which the protocol is being reviewed creates conflict of interest. Reviewing trial proposals for colleagues inevitably introduces an element of conflict of interest according to Emanuel (Emanuel et al., 2006).

In order to assess whether conflict of interest actually exists within RECs, we need to be clear about their primary and secondary interests. The primary interests for RECs include as mentioned earlier the protection of the welfare of potential participants from harm and exploitation and the assurance of their safety. The secondary interests may include financial gain and professional recognition and status. Hence in situations of conflict of interest the REC may perform actions permitted by their roles but which may not align with the enhancement of the primary interests of that role (Jonsen et al., 2006). RECs within developing countries need to be aware about the potential for conflict of interest and how it may affect their final decisions. Furthermore, they need to have clear policies about the declaration of conflict of interest and how it should be dealt with. It has to be emphasized however that the existence of conflict of interest itself does not make the decision of the REC unethical nor does it mean that the person involved or REC will give in to the conflict of interest, although the temptation may be hard to resist. It is the motivation created by the

conflict of interest that may cause one to act in ways that contradict with accepted responsibilities and disregard other peoples' interests. These factors causing the conflict of interest for the committee as a whole may under some circumstances provide powerful enough incentive to influence trial approvals in both the developing (Edejer, 1999) and developed world (Emanuel and Steiner, 1995; Kelch, 2002). Individual members of the REC may have conflicts of interests when it comes to certain trial proposals through either the personal knowledge or friendship with the researcher, or through the involvement with the sponsoring agency. Both these relationships may cloud the judgement of the individual member regarding the ethical appraisal of the trial proposal. When such situations exist, the member of the REC has to declare the existence of this conflict of interest in order for the REC as a whole to decide whether to allow that member to be present during the discussions of that specific trial proposal or to exclude him or her from these discussions. REC members also need to realize the influence of the institutions, sponsors, and developed countries on their role and not allow it to interfere with their primary function.

The other kind of conflict of interest relates to the researchers. The primary interest of the researchers is the performance of research and the generation of generalizable knowledge. However secondary interests may also co-exist with the primary interests such as financial gain and academic recognition. Researchers could be paid up to \$5000 per research participant recruited into a study (Benatar, 2002; Edejer, 1999). These kinds of figures instil strong motivation for recruiting trial participants and overlooking inclusion and exclusion criteria specified in the proposal. In such cases the researchers have to disclose the existence of the conflict of interest.

However, a simple disclosure may not be sufficient. Federman suggests that a committee other than the REC should handle the conflict of interest because its proper assessment demands more time and expertise than the REC has to give (Federman et al., 2002).

Federman argues that:

"Independent conflict of interest review by another entity within the programme is essential to ensure that such review is given appropriate attention, that any necessary conflict management plans are implemented, and that the relevant aspects of the review and management are communicated" (Federman et al., 2002: 82).

Once the REC receives a conflict of interest report it has to determine whether the conflict is acceptable when compared to the protection of potential participants. The review of conflict of interest is not restricted to financial conflict of interest, and can extend to look at the researcher's desire for professional advancement or scientific recognition. Furthermore, not all forms of conflict of interest should be prevented or be considered as unacceptable. The desire for professional advancement for example although it may be a potential source of conflict of interest may be considered as an acceptable form of conflict of interest. Given the academic settings today restricting advancements in professional status except with the presence of publications, it is no wonder that researchers, professionals, and academics strive to have publications under their name.

Proof of registration of the trial:

Prior to the approval of trials, RECs should require proof of registration of the proposed trials from the researchers. This is done for several reasons. To begin with, the REC, while performing its ethical review, can ensure that no replication of the trial takes place within the scientific or medical communities. If all trials are required to be registered, then comparisons between the different trials and their repetition aids in better directing resources and approval towards trials that address original scientific questions rather than repeated science. As argued earlier, this becomes the responsibility of the scientific review committee which is communicated to the REC rather than being the direct responsibility of the REC.

Furthermore, registration is sometimes confused with trial monitoring which is seen as one of the responsibilities of the REC. This task of continued monitoring is difficult to maintain by RECs mainly due to the lack of manpower and time required to keep up with the demand of this responsibility. Yet it cannot be denied that this issue is important for several reasons (Dickersin, 1992). Once a trial has been registered and approved, it can be monitored for indiscretions within the trial design as well analysis performance whenever necessary. Furthermore, continued monitoring may be done through the obligation of researcher to report adverse events and to provide the REC with regular update reports.

Another form of REC monitoring involves following the trial results to see if they have been published or not. Occasionally trial sponsors decide not to publish the trial results because of negative outcome, or unanticipated adverse events or side effects that lead to halting the trial. Keeping on top of the publication status helps the REC prevent future researchers or sponsors from performing the same trial, or a similar one that could inevitably expose trial

participants to risks previously known, but hidden from the rest of the scientific community. Researchers have an ethical duty to produce broadly useful knowledge and answer research questions. If researchers or sponsors conceal results every time they find negative results, or the intervention proves highly risky, then they fail to uphold this duty. Furthermore, repeating the same trials over and over again means redirecting precious resources away from what may turn out to be more beneficial trials. Therefore, RECs should demand evidence of trial registration prior to approving any trial (Harlan, 1994). In the United Kingdom for example, sponsors could register their trials in the National Research Registry (Chalmers et al., 1995). Having said that, and even with the importance of monitoring of trials in the post approval period, the RECs do not have the authority to enforce publication of trial results even if they wanted to. There needs to be regulations regarding this matter and even then a separate entity needs to follow up this matter other than the REC.

Therefore, from the previous discussions it has been shown that the main role of the REC is the prevention of unfair use of trial participants from both a procedural and outcome perspectives. The first one is established through the assurance that the requirements of informed consent are maintained. The second one is assured through the assurance of scientific value and validity which comes into play through interaction with another committee and the assurance of social value. In order to assess whether RECs are actually capable of fulfilling these responsibilities we need to focus on the formation of the different committees and then move on to discuss the discrepancies that might exist between the different RECs and whether these discrepancies can be justified or not.

The makeup of RECs:

Within developed countries, REC committee membership, although differing somewhat in the total number of members, includes qualified professionals as well as representatives from the public. In the United Kingdom for example, an NHS REC is made up of seven to eighteen volunteers with one-third membership comprised of people who have no professional interest in research or have not been involved in research except as participants (NHS). In the United States, a typical REC consists of five members at minimum, including both men and women from different professions. At least one member lacks scientific background and another bears no affiliation with the institution (CFR, 2005). Other countries such as France, Germany, and Norway have taken a national committee approach (Edwards et al., 2004). On the other hand within some developing countries, review boards do not exist (Voo et al., 2008; Kirigia et al., 2005). In cases where they do exist, the number of members on a given REC within developing countries varies considerably from three to thirty-one with an average of eleven members (Kass et al., 2007; Nyika et al., 2009). Most REC members (56%) have scientific or medical backgrounds, for example they may be pharmacists, nutritionists, or social scientists (Moodley and Myer, 2007). In South Africa 56% to 62% of the REC members are white males who are either scientists or clinicians (Moodley and Myer, 2007). The representation of females on these committees lies between 18% and 54% (Moodley and Myer 2007). Another study showed that these committees did not have any external members (Nyika et al., 2009). Public representation within these committees is very rare, amounting to only 8% in South Africa (Moodley and Myer, 2007). Other developing countries have established RECs or at least some form of ethical review process (Kennedy et

al., 2006; Effa et al., 2007). For example, Rivera in his work identified twenty RECs in Latin America (Rivera and Ezcurra, 2001) whereas in Central and Eastern Europe, Coker found ten countries that had national committees (Coker and McKee, 2001). The WHO Southeast Asian Regional office identified sixteen respondents with national RECs (WHO, 2002). South Africa houses approximately thirty-four local RECs, of which two are attached to private non-academic institutions (Moodley and Myer, 2007). The oldest REC in South Africa was established in 1967 and the one in Zimbabwe became formally established in 1992 (Kass et al., 2007).

From a general point of view, RECs in developed countries deserve credit on several fronts. For example, they maintain public representation on RECs so that consideration is given to public opinion about clinical trials. Those RECs are therefore, better equipped to handle public concerns locally at least given the number of public representation on these committees. The fact that these RECs include members not affiliated with the institution, from both sexes, and with different professional backgrounds, lends additional credibility to the REC's operation. The different professional background and makeup of these committees means that a wider perspective of opinions feed into the evaluation process. This approach serves its purpose especially when the intended study is to be carried out within the developed country itself, or in another developed country with similar traditions, customs, and beliefs. Careful selection of REC members ensures that customs and concerns, cultural norms, and cultural beliefs of the potential participants are considered and accounted for. In comparison, when we consider developing countries, this representation of public concerns and points of views are not expressed within the REC. In 2001, the World Health

Organization Regional Committee for Africa expressed concern over how studies are being carried out in the region without undergoing any form of ethical review (Kirigia et al., 2005). Therefore, there are concerns regarding the capability of RECs within developing countries to actually represent public opinions considering their current makeup.

Another shortcoming with RECs in developing countries relates to prior approval practices. Local RECs tend to approve a trial when it has already been formally approved in an industrialized country. This problem especially holds true for multicentre trials and has been discussed extensively by others (Butler, 2000; Wolffers, 1989). London states that:

"It is not uncommon for developing country IRBs to be pressured by funders or researchers to approve the local arm of a multicenter study that has already met with approval in the fender's home country" (London, 2002: 1079).

This pressure London refers to may result from differences in power established among various parties involved in the process i.e. the funders, researchers, governments, academic institutions, REC members in both developing and developed countries, and communities. Other published papers have expressed concerns regarding the rubber stamping of trial proposals by local RECs without consideration being given to local issues particularly for trials receiving international funding. Kass in her writings refers to researchers who state that "outsider researchers, and politicians could interfere with the REC process" while another suggests that the "culture of corruption is prevalent in some parts of Africa, which could affect the integrity of the committee" (Kass et al., 2007). Perhaps the REC members believe

wrongly so, that since the sponsoring country is much more advanced and has more expertise in assessing research proposals, there is really no need for the local REC to look at the proposal again. Even if this assumption holds true, it does not mean that the exact same trial will benefit the developing country in the same way, or meet its health care needs. The local RECs perhaps also worry that researchers failing to obtain a speedy approval may simply take their funds and research elsewhere.

Public representation on RECs:

RECs, whether in developed or developing countries, strive to ensure that they meet the anticipated role related responsibilities. One of the roles of the REC is to ensure that the best interest of the participants is served or at least does not become overpowered by the best interest of the researchers/sponsors. To do this, and to ensure that the potential participants are treated fairly by the researchers/sponsors, social value should be considered by the REC. Although this could be done by REC members if the REC was made up purely of members with scientific and medical backgrounds, these members' involvement within the scientific field, their professions, and affiliation with institutions sometimes blind them to some of the concerns that a lay person may have. If all REC members came from academic and professional staff also involved in research with human subjects, a potential for bias comes to the surface especially if we consider that REC members review proposals of their colleagues. Edwards stresses this point when she states:

“A bunch of doctors who may also be close friends and colleagues is not independent enough and certainly not of investigators generally

who may all be clouded by the same zeal of scientific innovation and material progress" (Edwards, 2009: 149).

Most scientists and professionals look for some form of recognition within the scientific society and hope to gain some advancement in their academic or professional status. Having research published under ones name or their institution is a great achievement and it is therefore, no wonder that all researchers, even those sitting on RECs want to encourage research in their own countries. Furthermore, although these professional members may at the same time be members of the public or community where the trial is intended to be carried out, their scientific or medical knowledge makes them down play or disregard the concerns of the public or to consider them as irrational, unrealistic, or unimportant. These settings do not mean that the best interest of the researcher/sponsor will take precedence over the best interest of the potential participants during the decision making process within the REC but rather that people from medical or scientific background tend to dismiss some of the concerns of the public based on their knowledge about the whole process as well as their field of practice. Kass argues:

"Some of the potential risks/ethics violations or cutting of corners can be perpetrated by collaborating investigators in other countries because the incentives to them (status, publications, foreign travel) to get the data collected are substantial enough as to be coercive" (Kass 2000, quoted in Macklin, 2004: 139)

It is no wonder then that these boards are sometimes accused of reflecting the researcher's point of view only. To aid RECs in performing their required roles, it has become recommended, or mandatory in some places, that people from the public should become permanent members on RECs. The idea behind the introduction of lay members on RECs is to ensure that people other than the scientists or researchers have assessed the acceptability of the risks involved. The lack of public representation on RECs carries the risk of biased decisions being made by professional REC members only (Emanuel and Steiner, 1995; Benatar, 2002). Lay members represent the concerns of their community or culture. Within RECs which serve culturally diverse communities, the lay members themselves have to represent the various communities served by that REC. In addition and in order to maximise the impact of these voices on final decisions made by RECs, the number of lay members on the RECs has to be large enough in order for their opinions not to be ignored. Their concerns and decisions have to have an impact on the final decision of the committee as a whole. The question that remains to be answered is who these public representatives should be. Do they need to come from lower socio-economic levels to represent the concerns of the population within those classes of society or could we allow any members of society without much concern to their socio-economic status? The purpose of having lay members on the REC is to ensure that the perspectives of the potential participants and their concerns are considered during the review process. Their role is not to assess the scientific value or validity of the trial proposal. They are required to assess the social value of the trial and assess the information sheets and informed consent forms. Appointing lay members from lower socio-economic levels could result in having members who do not have enough insight regarding the

concerns of the target population. Hence they may find it harder to fulfil their required responsibilities during the ethical appraisal of a given trial proposal. Those with higher levels of education may be better suited for this responsibility. For example, lawyers, ethics specialists, or even cancer survivors may be candidates to be considered as lay members on RECs. It is important to emphasise however that the focus of selection of public representatives on RECs should not be the level of education of these members but rather their independence from the institution within which the REC functions. This independence should be viewed from two perspectives; the first one is the independence from research. They should not be researchers themselves, or be related to any researchers. The only connection to research which may be permissible is their past involvement in research as trial participants. The second perspective of independence should be their independence from the institution to which the REC is attached. This independence should not exist either directly or indirectly meaning that the lay members should not be affiliated with the institution or be related to a member of that institution. Both these factors put together ensure that these members are not biased by their roles as researchers, connection to researchers, or their connection to the institution.

As committees within developing countries stand now, the number of expert members far exceeds the number of lay members. Therefore, if there was ever disagreement between the two sides, the expert side would overrule. If the input of lay members cannot have an impact on the decision of the committee then the whole process becomes self-defeating. We need to ensure that the outnumbering of lay members on the REC does not occur or is at least

minimized. Therefore the makeup of the REC should be reversed with more lay members being present than professionals since their input is crucial to REC decision.

It is important to stress here that lay people's perspectives should not only be considered but should have enough weight to shape the final decision of the REC. Hence, their presence as members within RECs is essential. In order to assess whether existing RECs in developed or developing countries are actually implementing this step, we need to consider the two settings separately.

RECs within developed countries:

To begin with, RECs in developed countries, especially the United Kingdom, have lay members on their committees which suits the purpose of reviewing research intended to be carried out locally since these lay members represent the concerns and perspectives of other lay members within that same setting. However, when these same RECs are required to assess research proposals intended to be carried out at distant locations, the role of these lay members needs to be questioned. It is important to remember that although humans share common concerns, especially those concerning health and perhaps education, different settings sometime bring about different priorities. For example, people who lack health care options may have very distinct priorities from those with access to more than minimal standards of health care. Furthermore, cultural, educational, and even religious differences put emphasis on varying aspects of health care services. How do the members of these RECs ensure that public interest, social, and cultural concerns are reflected within the review process?

Some RECs in developed countries have tried to manage these issues by instating a review member who is either knowledgeable about the culture of the hosting country, or who actually comes from that part of the world (Eckenwiler, 2001; Macpherson, 1999). This approach may prove to be inefficient. Maintaining expertise in each and every developing country concerned perhaps remains the biggest challenge to RECs because these countries form a heterogeneous group with different circumstances, conditions, cultural believes, and customs. Therefore it is impossible for one person to be knowledgeable in each and every population's preferences within these countries. Furthermore, these so called "lay member" would have been residing in the developed country for prolonged periods of times and may relate more to the cultural concerns of the population within the developed country than the country they originated from. In addition these so called experts usually represent people with higher levels of education and income (NCB, 1999), meaning that these members likely come from higher and more powerful social classes within the developing countries (White, 1999) and therefore, may not truly represent the concerns or needs of vulnerable populations recruited into the trial (Macpherson, 1999). In this case, participants' interests "filter through the eyes of consultants considered knowledgeable in participant affairs rather than by the populations themselves" (Lansang and Crawley, 2000). Furthermore, as argued above the use of single experts on RECs does not serve its purpose as a single member's opinion or input does not have much impact on the final decision made by the committee as a whole.

RECs within Developing countries:

RECs within developing countries have some problematic points that need to be highlighted as well. RECs within developing countries are mostly made up of members with scientific or medical backgrounds and rarely have lay members. Hence the same problems mentioned above regarding the exclusion of lay members from the review process and the problems it creates are reflected here as well. In addition to the lack of impact of lay members' votes on the final decision of the REC as a whole ranks as another problem with the makeup of these RECs.

If both setups have certain problematic areas when it comes to reviewing trial proposals intended to be carried out in developing countries, then we need to assess which setting would better serve the purpose of the review process.

Who should review the trial proposal?

The first option gives RECs in the sponsoring country the responsibility of ethical review, which makes sense because of the advanced experience of some RECs with these kinds of duties. However the problem with that approach is the lack of knowledge of the members of these RECs about the cultural concerns and beliefs of the target population. Although some committees have tried to overcome this issue, implementing this approach and allowing RECs within developed countries to review trial proposals intended to be carried out within developing countries, could prove very difficult. Finding someone knowledgeable in all matters concerning the diverse populations of developing countries could also prove highly challenging.

The second option gives the RECs within the developing countries that responsibility of assessing proposals for trials intended to be carried out within developing countries. This approach may be a much more acceptable one given the knowledge of the members within these committees about the local issue and the acceptability of the trial to the local population. Admittedly, this approach is also problematic considering, to begin with, the makeup of these committees as well as the lack of training of the members within these committees. However, with better training this difficulty may be overcome.

The third option, which may be seen as a temporary solution, could require both RECs within the sponsoring country and the developing countries to review any given trial proposal. This could be a temporary approach until RECs within developing countries receive the required training. The approach however could mean a longer review process from the perspective of the researchers/sponsors and delays in the communication of decisions made by these RECs (McMillan and Conlon, 2004). The advantages of such an approach though could be that the more experienced REC within the sponsoring country ethically appraises the proposal and thereby ensures research adherence to ethical standards. Whereas the local REC within developing countries addresses the local issues and the suitability of the trial to the local needs. Furthermore, developing countries RECs may recommend certain alterations which could make the trial proposal more suitable for local application. Having this type of structure in place means that the researchers may have to deal with longer processing times and delays in initiating the research, but other advantages ensue.

It has to be emphasised though that the ideal situation, and the one which I am calling for, is the review of trial proposals by local RECs within developing countries. Allowing local review

of the proposals can achieve two positive outcomes. First off, the review takes into account concerns of the community partaking in the research. This means that the trial itself is made more relevant to the health care needs of the community involved. Secondly, the RECs in the developing countries gain experience and competency through reviewing several trials. This increased level of skill among local RECs may benefit the researcher/sponsors as well. The local community's cooperation and the ability to recruit participants into the trial may not transpire without the help of local authorities. Establishing local trial support helps reassure participants that at least to some degree the trial will benefit their own health care setting and their community in general.

Discrepancies in REC decisions:

Still other accusations are linked to the discussion regarding the decisions made by RECs concerning trials intended to be carried out at distant (geographical or cultural) locations. This accusation is usually directed at the inconsistency between different REC decisions. It is noted that while some RECs may approve a given trial, another may request major changes, minor changes, or may reject a trial proposal all together. According to the NHS National Health Authority's recently published paper concerning consistencies in REC review (NHA 2014) there is a need to ensure that there is consistency between different RECs on two levels. The first one is the assurance that the different RECs are consistent from a procedural perspective and the second is the assurance of a consistency of content. The procedural consistency the document refers to is the assurance that different RECs not only follow the same ethical principles, but must also have similar structures and process. This means that in

order for us to ensure that different RECs are consistent we need to ensure that their structures are the same, they have roughly the same number, the member's expertise are the same, and they have access to the same information. On the other hand the consistency in content refers to the concept that REC needs to be consistent about the decisions it makes. An REC needs to make broadly the same decision when faced with a similar proposal in the future for broadly the same reasons it has used in the first instance. Although I agree with the second kind of consistency referred to by the NHS, I do not think that procedural consistency will eliminate the different decisions between RECs especially when considering geographically distant RECs. To clarify this problem, it will be viewed on two levels, the first one is the discrepancy between decisions of different local RECs within the same country or region and the second one focuses on the discrepancies between RECs within geographically distant countries. The first kind of discrepancies which focuses on differences between RECs located within the same geographical region or country but within different regions may be explained by the existence of minorities within a given region, cultural belief, or different interpretation and judgement of the proposal by the different members of the REC. The existence of these differing beliefs or customs will undoubtedly influence the decision of the REC. However the bulk of my discussion will focus on the second kind of discrepancies namely those between RECs within developed and developing countries.

Two papers have reported disagreements between RECs within developing countries and those located in developed countries, (Mfutso-Bengo and Taylor, 2002; Love and Fost, 2003). Other reports have shown differences in the way documents are reviewed concerning the two settings (Hyder et al., 2004). It is not surprising that these differences occur as different

countries have different policies or regulations, but there are other factors which may lead to these discrepancies. Ideally, ethical review of trial proposals should cover all the important ethical issues relevant to the proposal. There are certain circumstances where a given REC may accept the approval of another REC from an ethical perspective with special attention being given to issues regarding local implementation especially in multicentre trials intended to be carried out within different locations of the same country or different developed countries. However, special regard to this point should be made when the trial approved by an REC within a developed country is intended to be carried out in developing countries. This discrepancy between the decisions of different RECs may be justifiable despite the fact that consistent criteria are being implemented within the review process. The discrepancy itself may be due to several reasons other than the criteria being used. Some of these reasons stem from unfortunate circumstances, or what I would call correctable sources of discrepancies, which deserve to be improved and resurrected. However, it has to be stressed that even once these factors are corrected the discrepancy between the decisions of different RECs may still fail to be unified. This is because it is the second source of discrepancy which is more important. These reasons are seen as justifiable grounds for the differences in the decisions among different RECs. The first group of these reasons will be discussed initially.

Correctable sources of discrepancies:

The sources of discrepancies between different RECs' decisions may be traced back to reasons that once corrected may lead to the reduction of these discrepancies, or so it is

argued. One of these reasons could be related to the amount and kind of training the members of the REC receive. The lack of expertise to ethically assess research proposals represents a problem associated with RECs in developed as well as developing countries although the issue itself may exist on a larger scale within developing countries. According to several studies this problem mainly stems from insufficient training among REC members. For example, in one study in Tanzania, 49% of REC members reported having never received training in ethical review of health care research (Ikingura et al., 2007). Another study which looked at twelve African RECs revealed a lack of training among members and proposed this dilemma as one of the major challenges faced by the REC members in those countries. In Africa, 38% of REC members have never embarked on any formal training in the field of research ethics especially in the clinical area (Nyika et al., 2009). Hence if REC members within developing countries receive training regarding the ethical appraisal of trial proposals, the discrepancies between different RECs should be a rare occurrence. However this conclusion is misled since even when REC members receive training, it does not mean that the discrepancies in the final decisions between different committees will necessarily disappear. The kind of training the REC members need revolves around the ethical appraisal of trial proposals and the procedures and policies that govern the review process. Indeed some writers have even presented the idea that in some cases the training of the members may actually increase the discrepancies between the different RECs rather than reduce it. Edwards et al. present such an argument. They state:

“Indeed it may be that training increases differences, by making members more confident, more reflective and more inclined to see the issues from a variety of points of view” (Edwards et al., 2004: 414)

The broadened knowledge of the trained members about the principles and policies that govern their roles and the expectations attached to this role may indeed make the discussions among the different members more intense and may lead to further discrepancies among and between different RECs rather than unify them.

Another issue which may impact on the decision of the REC and may also be related to the lack of training of REC members is the conflict of interest which may influence the decisions of these committees. Some trial sponsors provide financial remuneration not only to the researchers but also to the institutions which approve their trials (Benatar, 2002; Edejer, 1999). These amounts could be very high and if REC members are not aware about the potential of conflict of interest and the powerful influence it may have on their decision, may lead them to approve trials which do not necessarily serve the potential participants interests. This situation may exist in both the developing (Edejer, 1999) and developed countries (Emanuel and Steiner, 1995; Kelch, 2002).

Other than training, mechanism of function of the REC may also have an effect on its decision. How the members interact with each other, the kind of discussions that take place and the general harmony between the members is another factor that causes different committees to reach different decisions. Furthermore, the simple existence of different people or members on different committees may be another reason for the different decisions. Individuals, regardless of receiving the same kind of training, may still reach

different decisions even when it comes to the same issue. How these individuals perceive the information and analyse it is different as is the case between any two or more people. This difference in decision making processes does not only occur within RECs. Scientific review board members may also disagree on specifics of trials despite the fact that they may come from the same backgrounds. It is important however to emphasise that the differences in decisions between different RECs be it at a local or international levels do not necessarily lead us to define these differences as being bad or morally problematic.

Justifiable reasons for discrepancies:

There are other reasons which may be the cause of the discrepancies between the decisions of different RECs. However, these reasons do not relate to the training level of the members or functionality of the REC. These discrepancies refer to the consideration of local issues which include cultural acceptance of the proposed trials to local needs. I have argued earlier that in order to ensure that potential participants are not exploited, the REC needs to assess the social value of the trial and the level of benefit to them. In order for this duty to be fulfilled, RECs need to make certain that exploitation does not occur or is minimised by ensuring that any given trial is acceptable to the potential participants' culture and that the trial will be socially valuable to them or to their communities.

Social value comes in several forms and relates to how the trial will benefit the hosting population or community. Some cultures may not find it acceptable for certain practices to take place within their communities or the concepts within the trial themselves may be difficult to comprehend by the concerned potential participants. To ensure that social value

receives proper consideration during a proposal review. We have presented in chapter three Emanuel et al.'s conditions for the assessment of social value within a trial (Emanuel et al., 2004). These included the determination of who will benefit from the trial results; the potential trial value to prospective beneficiaries, the target population's access to trial results, and the fact that the conduct of the trial should not undermine the existing health care system within the community.

The assessment of social acceptability and value of a given trial proposal to the community is best done by the people who come from these areas and understand the culture and belief of those people. The members of the REC who are mostly equipped to do this task are the lay members of the community who represent the general population. I have argued earlier that the numbers of these members have to be large enough in order for their comments and decisions to have an impact on the final decision of the REC. It is not enough that their concerns or fears are expressed and then ignored during the decision making process. We have also concluded earlier while assessing the makeup of the RECs in developed countries that having a single expert member to represent a community in developing countries' culture is not enough to be representative of the target population for several reasons. Therefore, the best approach is for trial proposals to be reviewed by local RECs.

Given that local lay members review trial proposals and have a say in whether it is acceptable to the local community, discrepancies between RECs, especially those from developed and developing countries are inevitable even if the same criteria for ethical review are followed. The source of this discrepancy is the social interpretation of how valuable the trial is to the community where it is intended to be carried out. This is a justifiable source of the

differences in the decisions of different RECs. If this point is taken into consideration, then it becomes clearer that even if we suggest uniform review processes and regulations between and among all RECs, the discrepancies in the decisions reached may not be affected by such a step given that cultural and social concerns are taken into consideration and are the main reason for these differences.

Allowing local review of the proposals can achieve two positive outcomes. First off, the review takes into account concerns of the community partaking in the research. This means that the trial itself is made more relevant to the health care needs of the community involved and certain changes which will make a proposal more applicable locally will be recommended. Secondly, the RECs in developing countries gain experience and competency through reviewing large number of trial proposal. This increased level of skill among local RECs may benefit researchers/sponsors by the assurance of participants that the trial will to some degree benefit them and their communities and therefore improve the local community's cooperation and recruitment of trial participants.

Conclusion:

This chapter has focused on the role of RECs in the process of prevention of exploitation. It was argued that local RECs should be given the responsibility of ethically assessing the acceptability of any given trial which will be performed locally. It has also been emphasised that the discrepancies between decisions of different RECs may be justifiable especially if we consider that social value is an important criteria in the ethical assessment of trial proposals. Reviewing research involving human subjects has always been a thorny topic and is especially

complicated by bad publicity related to research studies where subjects have been exposed to unnecessary harm or exploitation. The members of RECs should consider the welfare of all subjects on equal footing and protect them from potential harm and exploitation regardless of where they reside. The prevention of exploitation stems from two main areas. The first one stems from the assurance that the trial is fair to the potential participants from a procedural perspective. This is achieved through the proper review of how informed consent is to be obtained from the potential participants and what information they will be given to aid them in their decision making process. The second measure for the prevention of exploitation is the assurance of the social values of the trial to the community where it is intended to be carried out i.e. outcome fairness.

RECs come in different sizes and exist within different geographical areas and cultural settings. There are several accusations which RECs are accused of and they include the existence of conflict of interest and the focus of the members on the wording of the informed consent form rather than the communications process between the researchers and the potential participants. RECs are also accused of not paying enough attention to the social value of the trial to the local community, but perhaps the most important issue that deserves more attention is the representation of the voices and concerns of the public in the decision of the REC. Due to the widespread shift in performing trials within developing countries, RECs within industrialised countries are required to assess the acceptability of those trials to be performed on other less well-off communities. The RECs in sponsoring countries often have enhanced expertise and knowledge when it comes to ethically appraising trial proposals. Despite the fact the RECs within more developed countries may

have longer experiences at ethical review; their understanding of the local perspectives of the distant populations may not be optimal. This issue has been reconciled by most RECs in developed countries through seeking opinions from experts aware about local cultures and dilemmas. Yet this may be very difficult to perform in reality because of the diverse nature of beliefs and customs among developing countries populations. There may be difficulty in finding an expert in all of these cultures. In addition there may be difficulty in finding suitable representatives from each and every developing country. The most problematic issue though with such an approach, no matter how admirable it is, is that it can prove impractical due to the diversity of cultures and beliefs within developing countries. More importantly it needs to be emphasised that having a single expert on a committee made up from several other professional experts means that although the concerns of the public may be considered and heard by the committee, the voice of that expert does not have any effect on the final decision of the whole committee.

RECs in developing countries also have many problems starting from the composition of RECs extending to their lack of experience and training. They do however; hold a better awareness of local issues and the acceptability of the trial in their own setting. Yet most of these review boards are made up of professional scientists or people with a medical background. This approach means that the public's concern regarding any given trial renders the decision of the REC to be labelled as unrepresentative of the community. This relates directly to the fact that they are all professionals meaning that they can in some situations review the trial proposal from their professional perspectives rather than from the common local man's perspective. To ensure that the concerns of the average person within the community are

taken into consideration and affect the decision of the committee, two things need to be done. The first one is that lay members should be present on RECs. The second point is that they should make up the majority of the members. This approach ensures that the final decisions made truly represent what the public wants and not only what the professionals think should take place. Taking this point into consideration either on a local or an international level means that REC decisions may continue to be different and still not be considered as being problematic. If the public concerns are the main reason for these differences in decisions between and among RECs, then these different decisions should not be viewed as being problematic to either the researchers/sponsors.

We have also stressed the importance of local REC's making certain changes within their makeup to allow for more public representation on these committees and the need for these local committees to perform the ethical review of trial proposals intended to be carried out within their local community. This will not only allow them to take into consideration the perspectives of the potential participants but will also mean a broadening in their experience and capability in performing ethical reviews.

The take home message of this chapter is that despite the discrepancies in the final decisions made by different RECs, this fact alone does not mean that the decisions made by each REC is not rational or wrong in nature. We have to emphasise the fact that the true aim is to have more lay members on RECs than professionals. This needs to be done to ensure that the voice of the public which is represented in their points of views or comments is not overpowered by the positions or opinions of the professional members of the committee.

Chapter Six: Conclusion:

The thesis has recommended some new ways of thinking about the problem of exploitation in relation to research in developing countries. One of these concepts was the necessity to return to the essence of informed consent through the focus on communications rather than the legality of the form itself. Secondly, the acceptance of the possibility of the replacement of individual consent within some societies by that of the leader with certain precautions being taken into consideration as to whether or not community consent truly represents the choices and best interests of the community members. Furthermore, the adaptation of a broad post-trial benefit approach which includes a wide range of benefit not only to the trial participants but also to their communities. Fourthly, the concept of global research tax was endorsed and its importance emphasised. Finally, the recognition and acceptance of discrepancies between RECs within developing and industrialized countries was presented with an emphasis on the need to pay attention to the selection and makeup of these committee to include a majority of lay members rather than the current setup.

Over at least the last decade, the interest in the performance of clinical trials within developing countries and recruitment of participants from these counties has dramatically increased. Hence a lot of accusations were made against the sponsors of these clinical trials accusing them of exploiting the population of developing countries for their own benefit. It was necessary to examine this concept and come to an answer as to whether these trials were in fact exploiting their participants. In order to do so, the normative meaning of exploitation was used throughout this thesis. Exploitation was defined as the unfair use of

one person (or a group of people) by another. To truly understand what exploitation means we focused our discussions on what unfairness entails and looked at it from two different perspectives which have formed the basis of our discussion and analysis of exploitation. The first perspective was a procedural one which focused on how trial participants are enrolled into the trial, how much information they are given, the assessment of their level of understanding of the information provided by the research team, and the factors that may affect the level of understanding of the potential participants. Although some developing countries populations may have low levels of education and hold different beliefs regarding the causation of illness, it cannot be concluded automatically that informed valid consent cannot be obtained from these individuals. Nor could it be assumed that their levels of understanding of the information being presented to them cannot reach an acceptable level. Informed consent is best viewed as a process that takes place between two parties, the researchers and their teams and the potential participants. Labelling any consent as being "informed" demands that each party fulfils certain requirements. Researchers are required to ensure the competence of the potential participants, disclose certain information to them, ensure the potential participants understand the information presented to them, and ensure that the potential participants give their consent voluntarily. Some of the information the researchers must disclose to the potential participants include but are not exclusive to the purpose and duration of participation, the risks involved, freedom to withdraw from trial without penalty, available compensation of research related injury and the availability (or not) of post-trial access.

Although disclosing this information gives trial participants a fairly comprehensive overview of the trial details, it does not in-and-of-itself guarantee that the potential participant will actually understand all the information presented to them. Each participant has his own bench mark of required information needed to make an informed decision. Therefore, it was proposed that research teams should adopt an individualised approach when disclosing information to participants. It is the researcher's duty to make sure that potential participants actually understand the information presented to them. In order to do that, the researchers have to ensure that the potential participants are in the right mindset. They have to be in a deliberative mindset rather than an implementation mindset. This is an important step to undertake because it has been shown through empirical studies that potential participants tend to overestimate the chances of therapeutic or direct benefits to themselves and under estimate the risks involved if they are within the implementation mindset. Hence it is more important to focus on the validity of the participants' consent rather than how much information should be disclosed. Although achieving this goal means devoting extra time to potential participants and perhaps using local health care providers or patient advocates to ensure the proper translation of information is achieved, it can still be done and its importance should not be overlooked.

Perhaps a more problematic issue facing developing countries regarding informed consent is the higher importance given to community or tribal consent in lieu of individual consent. This approach may be seen as an aiding tool to the researchers as tribal or community leader consent by itself may enhance the recruitment of trial participants into the trial. Although this approach may differ from the method used in western countries, it does not mean that

the approach itself is wrong. Individuals within some of these developing countries' may view the provision of their individual consent as disrespectful to the community leader and may face negative social consequences from the community if they do so. To ensure that the community in general receives enough information about the trial without the researchers necessarily violating the community order, public meetings could be held between the researchers, community leaders, and community members where general essential information about the purpose and goal of the trial are presented to the community as a whole. Admittedly there may be situations where individual potential participants may decline participation in the trial and relay their choice to the researchers. In these cases, these potential participants could be excluded from the trial based on scientific or medical reasons. In other cases the community leader may not give permission for the trial to take place within that community. In such cases it would be very difficult to recruit individuals into the trial as individual consent has no value within these societies and researchers are perhaps better off relocating their trial to another community or country.

The second perspective of viewing unfairness is from an outcome perspective. The assessment of whether an interaction is exploitative or not is assessed based on how the parties are anticipated to gain at the end of their interaction with each other. Within any interaction between two or more parties, the outcome may include the parties not being affected, being harmed, or benefiting from the interaction. Given that trial benefit or harm is assessed prior to the interaction taking place, we have decided to look at each one of these outcomes from an ex-ante perspective; meaning that we will assess the anticipated outcomes based on the initial status of the individuals involved within the interaction. Trial

participants are rarely unaffected by their enrolment into the trial, hence the no effect option was not discussed. The participants may be harmed by their interaction with the researchers. Wendler's criteria were used for evaluating the risk-to-benefit ratio which includes three steps: (1) identifying the net-risk intervention, (2) assessing the net-risk intervention, and (3) assessing the net cumulative risk. It was also emphasised that the potential participant is the only person truly capable of assessing the acceptability of the potential risk. The level of harm could range from being minimal to serious. However, regardless of level of harm the assessment of the acceptability of the anticipated harm should be left to the potential participant given that different people accept different levels of harm. Therefore, even high risk trials may be allowed under the right circumstances and the importance of participant's autonomy and informed consent should be ensured through the process.

The anticipated benefit, on the other hand, is assessed from a different perspective: post-trial access and post-trial benefit. Post-trial access refers specifically to the provision of the proven intervention to the trial participants once the trial has ended, whereas post-trial benefits include other benefits which the potential participants and community may gain once the trial is over. Most of the arguments demanding post-trial access stem from the confusion between the roles of the health care providers and the researchers. Health care providers are supposed to act in the best interest of the patient because of the physicians' fiduciary responsibility towards their patients. Researchers on the other hand operate under a totally different set of rules. First of all, not all researchers are physicians meaning that the physician-patient model cannot be applied in all cases. Secondly, the aim of performing

clinical trials is to generate new knowledge aimed at improving the health of the general populations or future patients. The focus therefore falls on the whole community (either those suffering from a given medical condition or those belonging to a certain geographical region) rather than the individual patient. In this sense, the researcher-participant relationship is at best a morally contractual relationship which terminates after the trial has ended.

Researchers stand to gain from their interaction with the trial participants in many different ways. They may receive academic recognition for their work, get their research published, or gain financially. Sponsors of the trial also gain benefits most likely in a financial form through the marketing of their trial product once proven effective through the trial. Trial participants or their communities may also gain from their participation in a given trial.

The benefits that the trial participants stand to gain are numerous. These benefits were divided into direct, collateral, and aspirational benefits. Direct benefits include the perhaps most obvious benefit to the participants themselves which is the improvement in their health status. Collateral benefits come about as a result of the exposure of trial participants to extensive medical testing and follow up. This by itself may lead to the improvement in the health status of these individuals. Furthermore, given the importance of health to human beings and its view as a special kind of primary good, the improvement in health is a priceless goal to achieve regardless of any other benefits that the trial participants may gain during their participation in the trial. Aspirational benefits are the benefits that the community or future populations may enjoy such as the establishment of health care facilities, availability of equipment, or training of local health care providers.

Still despite the fact that the trial participants may benefit through their interaction with the researchers, the interaction itself may still be labelled as being exploitative and cases may exist where these interactions may justifiably be prohibited even when both parties involved stand to benefit from the interaction. Although several reasons are sometimes used to defend the prevention of mutually advantageous consensual exploitative interactions between the researchers/sponsors and the participants, most of them have been proven to be weak and unjustified. These arguments ranged from issues of degradation, to the expectations of trial participants, to instrumental use of the trial participants by the researchers/sponsors. Rather, the approach adopted for the justification of the prohibition of mutually advantageous consensual exploitative interactions was the strategic intervention. This approach basically requires the prohibition of exploitative interaction in order to promote better interaction for those who cannot do so for themselves.

Furthermore, post-trial benefit was introduced and how to best ensure that trial participants and their communities benefit fairly from the trial. To ensure a fair share of the benefits reaches the concerned individuals, the trial needs to address an issue that is important to the community where it is to be carried out i.e. it has to be socially valuable. Trial participants should be recruited for scientific reason and not for reasons such as convenience of the researchers/sponsors.

In addition to the improvement in the health of the individual participants, whole communities may gain through the training of local health care providers, the establishment of health care facilities, and other forms of capacity building.

To enhance other forms of collateral benefit, Ballantyne's idea of implementing a global research tax was adopted. Using Ballantyne's approach ensures that part of the sponsor's net profit gets redirected to maximize benefits to the less well-off within the relationship.

Finally, the role of the RECs in the whole process of exploitation of trial participants was discussed. Perhaps the most experienced RECs existing today are located in developed countries. These RECs have gained wider experience in the field due to the sheer number of trials they review on a regular basis, and also because their members are well trained and knowledgeable about issues that come under heavy scrutiny during a trial review. Problems occur when these RECs within developed countries are required to evaluate trials intended to be carried out in distant developing countries. Here the REC may not be fully aware of the issues considered unacceptable by the local population. Although some RECs make an extra effort to understand local population perspectives by consulting an expert in the field or someone who originally comes from that region, this approach does not always work in practice because of developing countries' diversity as well as the lack of influence that one person has on the final decision of the REC. Trial proposals should be reviewed by local RECs within developing countries with the structure of these boards being revised to include more lay members than professionals. This is an extremely important point to consider given that most professionals tend to dismiss some of the concerns of the public due to their professional roles despite them being members of that same community. The most common accusation directed at RECs is the discrepancies in the decisions made by different RECs. This was not seen as a problematic issue especially when considering the input of lay members and consideration of local issues and concerns that feed into the final decision of the REC.

These differences may not even disappear with more training of the REC members. In fact the differences may increase with this training. The point is not the eradication of all differences but the increased consideration and input of the public and community concerned.

The whole aim of focusing on a broader perspective of post-trial benefits and the social value of the trials to the concerned communities is to improve the current existing conditions within developing countries. By better training of local health care providers, availability of health care facilities and equipment, and focusing clinical trials on socially relevant health care issues, the 10/90 gap will be reduced. This can be achieved through the increased expenditure on research aimed at the discovery of treatments for illnesses devastating these areas. Through the performance of these trials other benefits may be gained such as the establishment of health care facilities and the provision of equipment by the sponsors of the trial. This provision of several kinds of benefits and the focus on social value mean that the trial participants are not being exploited by the researchers/sponsors. On the contrary, by the insistence on these issues, it is ensured that the populations of developing countries are recruited into trials for their populations' or community's anticipated benefit.

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